```
=> d his

     (FILE 'HOME' ENTERED AT 09:00:42 ON 14 MAR 2002)
               SET COST OFF

     FILE 'REGISTRY' ENTERED AT 09:01:01 ON 14 MAR 2002
               E FILAGGRIN
L1           6 S E3
L2          10 S ?FILAGGRIN?/CNS
L3          10 S L1,L2

     FILE 'HCAPLUS' ENTERED AT 09:01:52 ON 14 MAR 2002
               E FILAGGRIN
L4         325 S E3-E5
L5           4 S E11
L6         326 S L4,L5
               E FILAGGRIN/CT
               E E3+ALL
L7         240 S E4,E5,E3+NT
               E FILAGGRIN/CT
L8          31 S E4,E5
               E E4_ALL
               E FILAGGRIN/CT
               E E4+ALL
L9          81 S E4-E6
L10        339 S ?FILAGGRIN?
L11        340 S L6-L10
L12          8 S L3
L13        341 S L11,L12
               E SERRE G/AU
L14         40 S E3-E5
               E GIRBAL NEUHAUSER E/AU
L15         10 S E3,E4
               E GIRBAL E/AU
L16          4 S E3,E4
               E NEUHAUSER E/AU
L17          9 S E3,E4
L18          5 S E10
               E VINCENT C/AU
L19        360 S E3-E14,E32,E33
               E SIMON M/AU
L20        826 S E3-E28
               E SIMON MICHEL/AU
L21         94 S E3-E6
               E SEBBAG M/AU
L22         18 S E3,E4
               E DALBON P/AU
L23         26 S E3-E5
               E JOLIVET REYNAUD C/AU
L24         37 S E3,E4,E1
               E JOLIVET C/AU
L25          5 S E3
L26          1 S E53
               E REYNAUD C/AU
L27         76 S E3,E4,E12
               E ARNAUD M/AU
L28        147 S E3-E9,E20
               E JOLIVET M/AU
L29         92 S E3,E4,E8,E9
               E  BIOMOERIEUX/PA,CS
               E  BIOMERIEUX/PA,CS
L30        195 S E3-E36
L31        134 S (BIO(L)MERIEUX)/PA,CS
L32         21 S L13 AND L14-L31
L33          8 S L32 AND ?CITRUL?
L34          4 S L32 AND ARGIN?
```

Jan Delaval
Reference Librarian
Biotechnology & Chemical Library
CM1 1E07 – 703-308-4498
jan.delaval@uspto.gov

```
L35           0 S L32 AND (CIT OR ARG)

     FILE 'REGISTRY' ENTERED AT 09:12:02 ON 14 MAR 2002
L36           2 S ARGININE/CN
L37           1 S D-ARGININE/CN
L38           1 S CITRULLINE/CN
L39           2 S (DL-CITRULLINE OR D-CITRULLINE)/CN

     FILE 'HCAPLUS' ENTERED AT 09:12:47 ON 14 MAR 2002
L40       31077 S L36-L39
L41           4 S L40 AND L32
L42           8 S L33,L34,L41
L43          14 S L13 AND L40
L44          26 S L13 AND (CIT OR ?CITRUL?)
L45          27 S L13 AND (ARG OR ARGIN?)
L46          17 S L44 AND L45
L47          23 S L43,L46
L48          13 S L43-L45 NOT L47
L49          36 S L42-L48
L50          30 S L13 AND ?RHEUMAT?
L51          30 S L13 AND ?ARTHRIT?
                E RHEUMAT/CT
                E E19+ALL
L52        8601 S E9,E10,E8+NT
                E E19+ALL
L53        1292 S E4
                E E6+ALL
L54       16375 S E5+NT
                E E4+ALL
L55       18146 S E4,E5,E3+NT
L56          26 S L13 AND L52-L55
L57          30 S L50,L51,L56
L58          28 S L13 AND AUTOANTIBOD?
L59           7 S L13 AND AUTO(L)ANTIBOD?
                E AUTOANTIBOD/CT
                E E4+ALL
L60           8 S E1 AND L13
L61          13 S E2 AND L13
L62           9 S AUTOANTIB?/CW AND L13
L63          91 S ?ANTIBOD? AND L13
L64          91 S L58-L63
L65         110 S L57,L64,L49
L66          80 S L65 AND (PY<=1998 OR PRY<=1998 OR AY<=1998)
L67          21 S L66 AND L49
L68          16 S L66 AND L57
L69          68 S L66 AND L64
L70          19 S L69 AND L67,L68
L71          31 S L67,L68,L70
L72          14 S L32 AND (PY<=1998 OR PRY<=1998 OR AY<=1998)
L73          35 S L71,L72
L74           7 S L32 NOT L73
L75          35 S L73 AND L4-L74
L76           7 S L74 AND L4-L75

=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 09:22:24 ON 14 MAR 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2002 AMERICAN CHEMICAL SOCIETY (ACS)
```

FILE COVERS 1907 - 14 Mar 2002 VOL 136 ISS 11
FILE LAST UPDATED: 12 Mar 2002 (20020312/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

The P indicator for Preparations was not generated for all of the CAS Registry Numbers that were added to the CAS files between 12/27/01 and 1/23/02. As of 1/23/02, the situation has been resolved. Searches and/or SDIs in the H/Z/CA/CAplus files incorporating CAS Registry Numbers with the P indicator executed between 12/27/01 and 1/23/02 may be incomplete. See the NEWS message on this topic for more information.

=> d 175 bib abs hitrn retable tot

L75 ANSWER 1 OF 35 HCAPLUS COPYRIGHT 2002 ACS
AN 1999:785829 HCAPLUS
DN 132:11629
TI Peptide epitopes recognized by **antifilaggrin auto-antibodies** present in serum of **rheumatoid arthritis** patients and their use in diagnosis
IN **Serre, Guy Bruno Rene; Girbal Neuhauser, Elisabeth; Vincent, Christian; Simon, Michel; Sebbag, Mireille; Dalbon, Pascal; Jolivet Reynaud, Colette ; Arnaud, Michel; Jolivet, Michel**
PA **Bio Merieux** S. A., Fr.
SO Fr. Demande, 21 pp.
CODEN: FRXXBL
DT Patent
LA French
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	FR 2773157	A1	19990702	FR 1997-16673	19971230 <--
	FR 2773157	B1	20011005		
	WO 9935167	A1	19990715	WO 1998-FR2899	19981229 <--
	W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9919717	A1	19990726	AU 1999-19717	19981229 <--
	EP 1042366	A1	20001011	EP 1998-964536	19981229 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PRAI	FR 1997-16673	A	19971230 <--		
	WO 1998-FR2899	W	19981229 <--		

AB **Citrulline**-contg. peptides recognized by **autoantibodies** from the serum of patients with **rheumatoid arthritis** are disclosed. These peptides may be used in immunoassays for detection of these **autoantibodies** and for diagnosis of this disease. Thus, expts. showed that **citrulline**-contg. peptide 71-119 of human **filaggrin** reacted with the **autoantibodies** of **rheumatoid arthritis** patients while the same peptide, in

which the **arginine** residue had not been converted to **citrulline** by the action of peptidyl **arginine** deiminase, did not react. Two 14-amino acid **citrulline**-contg. peptides which also are recognized by these **autoantibodies** were prepd.

L75 ANSWER 2 OF 35 HCAPLUS COPYRIGHT 2002 ACS
AN 1999:785823 HCAPLUS
DN 132:444
TI Use of **filaggrin**-derived **citrulline**-containing peptides for treatment of **rheumatoid polyarthritis**
IN **Serre, Guy Bruno Rene; Girbal Neuhauser, Elisabeth; Vincent, Christian; Sebbag, Mireille; Simon, Michel; Dalbon, Pascal; Jolivet Reynaud, Colette; Arnaud, Michel; Jolivet, Michel**
PA Universite Paul Sabatier Toulouse III, Fr.
SO Fr. Demande, 25 pp.
CODEN: FRXXBL
DT Patent
LA French
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	FR 2773078	A1	19990702	FR 1997-16672	19971230 <--
	FR 2773078	B1	20000526		
	WO 9934819	A2	19990715	WO 1998-FR2900	19981229 <--
	WO 9934819	A3	19991104		
	W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9919718	A1	19990726	AU 1999-19718	19981229 <--
	EP 1041997	A2	20001011	EP 1998-964537	19981229 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, NL, SE, IE, FI				
	JP 2002500195	T2	20020108	JP 2000-527267	19981229 <--
PRAI	FR 1997-16672	A	19971230 <--		
	WO 1998-FR2900	W	19981229 <--		

AB Antigenic peptides derived from **filaggrin**, and in which at least one **arginine** residue has been replaced by a **citrulline** residue, are used for the prepn. of medicaments for the treatment of **rheumatoid polyarthritis**.
IT **372-75-8, Citrulline**
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(**arginine** replacement by; **filaggrin**-derived **citrulline**-contg. peptides for treatment of **rheumatoid polyarthritis**)
IT **74-79-3, L-Arginine**, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**citrulline** replacement for; **filaggrin**-derived **citrulline**-contg. peptides for treatment of **rheumatoid polyarthritis**)

L75 ANSWER 3 OF 35 HCAPLUS COPYRIGHT 2002 ACS
AN 1999:380965 HCAPLUS
DN 131:31040
TI Synthetic peptides containing **citrulline** recognized by **rheumatoid arthritis** sera as tools for diagnosis and treatment
IN Meheus, Lydie; Union, Ann; Raymackers, Joseph
PA Innogenetics N.V., Belg.
SO PCT Int. Appl., 74 pp.
CODEN: PIXXD2
DT Patent

LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9928344	A2	19990610	WO 1998-EP7714	19981130 <--
	WO 9928344	A3	19990812		
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	EP 949270	A1	19991013	EP 1998-870078	19980409 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	AU 9921558	A1	19990616	AU 1999-21558	19981130 <--
	EP 1034186	A2	20000913	EP 1998-965715	19981130 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
PRAI	EP 1997-870195	A	19971128 <--		
	EP 1998-870078	A	19980409 <--		
	WO 1998-EP7714	W	19981130 <--		

AB The present invention relates to a method of producing certain peptides contg. **citrulline** residues that constitute immunogenic determinants of **antibodies** present in sera from patients with **rheumatoid arthritis** and wherein the presence of at least one **citrulline** is a prerequisite for reacting with said **antibodies**. The invention also relates to a method of producing said **antibodies** and the use of said peptides for diagnosis and treatment of **rheumatoid arthritis**. The **citrulline**-contg. peptides, may be circularized or branched peptides and/or contg. tandem repeats, are derived from variant of **filaggrin**, intermediate filament protein, vimentin, cytokeratin 1 or cytokeratin 9.

IT **372-75-8, Citrulline**
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(synthetic peptides contg. **citrulline** recognized by **rheumatoid arthritis** sera as tools for diagnosis and treatment)

L75 ANSWER 4 OF 35 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:700033 HCAPLUS
DN 130:50364
TI Deimination of 70-kD nuclear protein during epidermal apoptotic events in vitro
AU Mizoguchi, Masayuki; Manabe, Motomu; Kawamura, Yasushi; Kondo, Yukiko; Ishidoh, Kazumi; Kominami, Eiki; Watanabe, Kazutaka; Asaga, Hiroaki; Senshu, Tatsuo; Ogawa, Hideoki
CS Department of Dermatology, Tokyo Metropolitan Institute of Gerontology, Juntendo University School of Medicine, Tokyo, 113, Japan
SO J. Histochem. Cytochem. (**1998**), 46(11), 1303-1309
CODEN: JHCYAS; ISSN: 0022-1554
PB Histochemical Society, Inc.
DT Journal
LA English
AB Peptidylarginine deiminase (PAD) is the enzyme responsible for converting protein-bound **arginine** residues to **citrulline**. It has recently been shown that a no. of epidermal proteins, including **filaggrin**, trichohyalin, and keratins, are deiminated by the action of PAD, suggesting a possible role for protein deimination during the final stages of epidermal differentiation. We report here a novel PAD substrate found during the course of identifying deiminated proteins in cultured rat epidermal keratinocytes. We found that a 70-kD protein

localized to the periphery of the nucleus was preferentially deiminated after ionomycin treatment in the presence of 2 mM calcium and was assocd. with apoptotic events in these cells. Furthermore, we discovered that the deimination of nuclear protein could be induced by transfection of a PAD cDNA into rat epidermal keratinocytes. These data suggest that PAD may act on the 70-kD nuclear protein to induce disassembly of the nuclear lamina and promote apoptosis during terminal epidermal differentiation.

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Ellis, L	1986	45	721	Cell	HCAPLUS
Gavrieli, Y	1992	119	493	J Cell Biol	HCAPLUS
Harding, C	1983	170	651	J Mol Biol	HCAPLUS
Imparl, J	1995	318	370	Arch Biochem Biophys	HCAPLUS
Ishigami, A	1996	223	299	Biochem Biophys Res	HCAPLUS
Luo, S	1995	318	362	Arch Biochem Biophys	HCAPLUS
Martin, J	1995	82	349	Cell	
Mastronardi, F	1996	97	349	J Clin Invest	HCAPLUS
Merchenthaler, I	1989	37	1563	J Histochem Cytochem	HCAPLUS
Rogers, G	1963	11	700	J Histochem Cytochem	HCAPLUS
Rogers, G	1997	108	700	J Invest Dermatol	HCAPLUS
Rothnagel, J	1984	107	624	Methods in Enzymolog	HCAPLUS
Senshu, T	1992	203	94	Anal Biochem	HCAPLUS
Senshu, T	1996	225	712	Biochem Biophys Res	HCAPLUS
Senshu, T	1995	105	163	J Invest Dermatol	HCAPLUS
Terakawa, H	1991	110	661	J Biochem (Tokyo)	HCAPLUS
Tsuchida, M	1993	215	677	Eur J Biochem	HCAPLUS
Watanabe, K	1988	966	375	Biochim Biophys Acta	HCAPLUS
Watanabe, K	1989	264	15255	J Biol Chem	HCAPLUS
White, E	1996	10	1	Genes Dev	HCAPLUS

L75 ANSWER 5 OF 35 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:394711 HCAPLUS
DN 129:188241
TI Correlation between anti-RA33/36 **antibody**, anti-keratin **antibody** and anti-perinuclear factor in **rheumatoid arthritis** patients
AU Tian, Xinping; Jiang, Ming; Song, Qinfang; Li, Yongzhe; Cui, Jingtao
CS Peking Union Med. College Hosp., PUMC, CAMS, Beijing, 100730, Peop. Rep. China
SO Zhonghua Weishengwuxue He Mianyixue Zazhi (**1998**), 18(2), 135-137
CODEN: ZWMZDP; ISSN: 0254-5101
PB Weishenbu Beijing Shengwu Zhipin Yanjiuso
DT Journal
LA Chinese
AB Three **auto-antibodies**, anti-RA33/36 **antibody**, anti-keratin **antibody** (AKA), and anti-perinuclear factor (APF) in the sera of 45 **rheumatoid arthritis** (RA) patients were tested by Western-blot assay and indirect immunofluorescence method. The assocn. between these **antibodies** was assessed. The results showed the pos. rates of anti-RA33/36 **antibody**, AKA, and APF were 35.6% (16/45), 31.3% (14/45), and 53.3% (24/45), resp. Thus, no significant correlation could be found between these **autoantibodies** although they could be present in RA patients simultaneously.

L75 ANSWER 6 OF 35 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:352872 HCAPLUS
DN 129:40127
TI Peptide derived from an antigen recognized by **autoantibodies** from patients with **rheumatoid arthritis**, **antibody** directed against said peptide, a combinatorial antigen, and a method of detecting autoimmune **antibodies**
IN Van Venrooij, Waltherus Jacobus Wilhelmus; Schellekens, Gerardus Antonius; Raats, Jozef Maria Hendrik; Hoet, Rene Michael Antonius

PA Stichting Scheikundig Onderzoek Nederland, Neth.; Stichting voor de Technische Wetenschappen; Van Venrooij, Waltherus Jacobus Wilhelmus; Schellekens, Gerardus Antonius; Raats, Jozef Maria Hendrik; Hoet, Rene Michael Antonius
SO PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DT Patent
LA Dutch
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9822503	A2	19980528	WO 1997-NL624	19971114 <--
	WO 9822503	A3	19980827		
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	NL 1004539	C2	19980520	NL 1996-1004539	19961115 <--
	AU 9749707	A1	19980610	AU 1997-49707	19971114 <--
	AU 741850	B2	20011213		
	EP 941244	A2	19990915	EP 1997-912577	19971114 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	BR 9712955	A	19991207	BR 1997-12955	19971114 <--
	JP 2001513753	T2	20010904	JP 1998-523501	19971114 <--
PRAI	NL 1996-1004539	A	19961115 <--		
	WO 1997-NL624	W	19971114 <--		

AB The invention relates to a peptide derived from an antigen (i.e. **profilaggrin** or **filaggrin**) recognized by **autoantibodies**, which peptide is reactive with autoimmune **antibodies** from a patient suffering from **rheumatoid arthritis**. The peptide according to the invention possesses a modified **arginine** residue. The invention also relates to **antibodies** against the peptide and a method of detecting autoimmune **antibodies**.

L75 ANSWER 7 OF 35 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:320407 HCAPLUS
DN 129:107919
TI Diagnostic value of **antibodies** to **filaggrin** in **rheumatoid arthritis**
AU Slack, Shawn L.; Mannik, Mart; Dale, Beverly A.
CS Division of Rheumatology and the Department of Oral Biology, University of Washington School of Medicine and School of Dentistry, University of Washington, Seattle, WA, 98195-6428, USA
SO J. Rheumatol. (**1998**), 25(5), 847-851
CODEN: JRHUA9; ISSN: 0315-162X
PB Journal of Rheumatology Publishing Co. Ltd.
DT Journal
LA English
AB The objective of this study was to det. the prevalence of **antibodies** to **filaggrin** in a cross sectional sample of patients with **rheumatoid arthritis** (RA). **Filaggrin** from human skin was either extd. with 0.05% Nonidet P-40 and then partially purified by pptg. in ethanol and resuspending in water (Nonidet prepn.) or extd. with 9 M urea and then purified by sequential fractionation on a DEAE Sephadex column and on a strong cation exchange column (purified prepn.). **Antibodies** to **filaggrin** were detected using immunoblotting techniques with sera dild. 1:50. Antikeratin **antibodies** (AKA) were detected using indirect immunofluorescence microscopy on sections of rat esophagus. **Antibodies** to **filaggrin** were detected in 5 of 30 sera of

patients with RA using **filaggrin** from the Nonidet prepn. and 6 of 49 sera using **filaggrin** from the purified prepn. AKA were detected in 13 of 40 sera. A pos. correlation existed between the presence of AKA and the presence of **antibodies** to **filaggrin** using the purified prepn. (p=0.017). These data indicate that the reactivity of RA sera with **filaggrin** is not identical to the presence of AKA and is variable depending upon the prepn. of **filaggrin** used. The diagnostic value of **antibodies** to **filaggrin** remains to be proven.

L75 ANSWER 8 OF 35 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:320406 HCAPLUS
DN 129:107700
TI Immunoblotting detection of **autoantibodies** to human epidermis **filaggrin**: a new diagnostic test for **rheumatoid arthritis**
AU **Vincent, Christian; Simon, Michel; Sebbag, Mireille; Girbal-Neuhauser, Elisabeth;** Durieux, Jean-Jacques; Cantagrel, Alain; Fournie, Bernard; Mazieres, Bernard; **Serre, Guy**
CS Department of Biology and Pathology of the Cell, INSERM CJF 96-02 Purpan Medical School, University of Toulouse III, Toulouse, Fr.
SO J. Rheumatol. (**1998**), 25(5), 838-846
CODEN: JRHUA9; ISSN: 0315-162X
PB Journal of Rheumatology Publishing Co. Ltd.
DT Journal
LA English
AB We previously reported that so-called antikeratin **antibodies** (AKA) and antiperinuclear factor (APF) recognize epitope(s) present on human epidermal **filaggrin**. In the present study, we developed a new diagnostic test for **rheumatoid arthritis** (RA) based on detection of **antifilaggrin autoantibodies** (AFA) by immunoblotting. We tested 670 serum samples, including 190 RA. AFA titers were estd. by immunoblotting on **filaggrin** enriched human epidermis exts., and AKA titers by indirect immunofluorescence (IIF) on rat esophagus epithelium. Diagnostic values of the tests were compared. Each test resulted in diagnosis of more than 40% of RA samples, with a specificity of 0.99. Although the tests were strongly correlated, their assocn. allowed the diagnosis of more than 60% of RA samples, with the same specificity. Immunoblot detection of AFA, a simple and standardizable test, may be an alternative or complement to conventional IIF detection of AKA.

L75 ANSWER 9 OF 35 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:302164 HCAPLUS
DN 129:94086
TI Purification of **filaggrin** from human epidermis and measurement of **antifilaggrin autoantibodies** in sera from patients with **rheumatoid arthritis** by an enzyme-linked immunosorbent assay
AU Palosuo, T.; Lukka, M.; Alenius, H.; Kalkkinen, N.; Aho, K.; Kurki, P.; Heikkila, R.; Nykanen, M.; Von Essen, R.
CS Lab. Immunobiol., Natl. Public Health Inst., Helsinki, FIN-00300, Finland
SO Int. Arch. Allergy Immunol. (**1998**), 115(4), 294-302
CODEN: IAAIEG; ISSN: 1018-2438
PB S. Karger AG
DT Journal
LA English
AB The so-called anti-keratin **antibody** (AKA) and the anti-perinuclear factor (APF) that recognize proteins related to human epidermal **filaggrin** belong to the most specific serol. markers of **rheumatoid arthritis** (RA). However, assays for the detection of AKA and APF are currently based on immunofluorescence, a method that is subject to arbitrary interpretation and inadequate standardization of the substrates. Proteins extd. from human epidermis were sepd. by reversed-phase high-performance liq. chromatog. (HPLC).

Filaggrin-contg. fractions, identified in immunoblotting by monoclonal anti-**filaggrin antibodies**, were then subjected to gel filtration HPLC and, finally, to a second reversed-phase HPLC step. Tryptic digestion, amino acid sequencing and mass spectrometry were used to confirm the identity of the purified protein. **Filaggrin** was used as antigen in ELISA to measure IgG class anti-**filaggrin antibodies**. The **filaggrin** prepn. obtained gave a single band in SDS-PAGE, binding monoclonal anti-**filaggrin antibody** in immunoblotting. Amino acid sequences of all 10 tryptic peptides analyzed were shown to originate from human **filaggrin**. Anti-**filaggrin antibody** levels exceeded the 99th percentile level of 100 middle-aged blood donors in 26/55 (47%) RA sera. At a similar cutoff level 28/55 (51%) of the RA sera were pos. in the AKA test. Of the 26 anti-**filaggrin**-pos. sera, 21 were also AKA-pos. Human **filaggrin** can be purified by std. biochem. techniques, despite the heterogeneity of the protein, and used in ELISA for testing **autoantibodies** to **filaggrin**. The sensitivity of the assay equals that of the AKA test.

L75 ANSWER 10 OF 35 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:163682 HCAPLUS
DN 128:229350
TI **Citrulline**-containing antigens derived from **filaggrin** and their use for diagnosing **rheumatoid polyarthritis**
IN **Serre, Guy; Girbal-Neuhauser, Elisabeth; Vincent, Christian; Simon, Michel; Sebbag, Mireille; Dalbon, Pascal; Jolivet-Reynaud, Colette; Arnaud, Michel; Jolivet, Michel**
PA **Biomerieux, Fr.**; Serre, Guy; Girbal-Neuhauser, Elisabeth; Vincent, Christian; Simon, Michel; Sebbag, Mireille; Dalbon, Pascal; Jolivet-Reynaud, Colette; Arnaud, Michel; Jolivet, Michel
SO PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DT Patent
LA French
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9808946	A1	19980305	WO 1997-FR1541	19970901 <--
	W: CA, US				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	FR 2752842	A1	19980306	FR 1996-10651	19960830 <--
	FR 2752842	B1	19981106		
	EP 929669	A1	19990721	EP 1997-938965	19970901 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
PRAI	FR 1996-10651		19960830 <--		
	WO 1997-FR1541		19970901 <--		

AB The invention concerns an artificial antigen specifically identified by the anti-**filaggrin autoantibodies** present in the serum of patients suffering from **rheumatoid polyarthritis**, and consisting of one polypeptide comprising all or part of the sequence of one **filaggrin** unit or of a related mol., in which an **arginine** residue has been substituted by a **citrulline** residue. The invention also concerns the use of this antigen for diagnosing **rheumatoid polyarthritis**. Peptides corresponding to human **filaggrin** residues 71-119 as well as tetradecapeptides EQSADSSRHSGSGH and ESSRDGSRHPRSHD were synthesized and treated with peptidyl **arginine** deiminase to convert the **arginyl** residues to **citrullinyl** residues. These peptides reacted with sera from patients suffering from **rheumatoid polyarthritis**.
IT **372-75-8, Citrulline**
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(**citrulline**-contg. antigens derived from **filaggrin** and their use for diagnosing **rheumatoid polyarthritis**

)

L75 ANSWER 11 OF 35 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:31000 HCAPLUS
DN 128:139653
TI **Citrulline** is an essential constituent of antigenic determinants recognized by **rheumatoid arthritis**-specific **autoantibodies**
AU Schellekens, Gerard A.; De Jong, Ben A. W.; Van Den Hoogen, Frank H. J.; Van De Putte, Leo B. A.; Van Venrooij, Walther J.
CS Department of Biochemistry, University of Nijmegen, Nijmegen, 6500 HB, Neth.
SO J. Clin. Invest. (**1998**), 101(1), 273-281
CODEN: JCINAO; ISSN: 0021-9738
PB Rockefeller University Press
DT Journal
LA English
AB Only a few **autoantibodies** that are more or less specific for RA have been described so far. The **rheumatoid** factor most often tested for is not very specific for RA, while the more specific antiperinuclear factor for several reasons is not routinely used as a serol. parameter. Here the authors show that **autoantibodies** reactive with synthetic peptides contg. the unusual amino acid **citrulline**, a posttranslationally modified **arginine** residue, are specifically present in the sera of RA patients. Using several **citrulline**-contg. peptide variants in ELISA, **antibodies** could be detected in 76% of RA sera with a specificity of 96%. Sera showed a remarkable variety in the reactivity pattern towards different **citrulline**-contg. peptides. Affinity-purified **antibodies** were shown to be pos. in the immunofluorescence-based antiperinuclear factor test, and in the so-called antikeratin **antibody** test, and were reactive towards **filaggrin** extd. from human epidermis. The specific nature of these **antibodies** and the presence of these **antibodies** early in disease, even before other disease manifestations occur, are indicative for a possible role of **citrulline**-contg. epitopes in the pathogenesis of RA.
IT **372-75-8**, L-**Citrulline**
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(**citrulline** is essential constituent of antigenic determinants recognized by **rheumatoid arthritis** -specific **autoantibodies**)

L75 ANSWER 12 OF 35 HCAPLUS COPYRIGHT 2002 ACS
AN 1997:454000 HCAPLUS
DN 127:62876
TI Immortalized human skin cell lines and serum-free medium for their culture
IN Baur, Markus; Mace, Catherine; Malnoe, Armand; Pfeifer, Andrea M. A.; Regnier, Marcelle
PA Societe Des Produits Nestle S.A., Switz.
SO Eur. Pat. Appl., 27 pp.
CODEN: EPXXDW
DT Patent
LA French
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 780469	A1	19970625	EP 1996-203641	19961219 <--
	EP 780469	B1	20010228		
	R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	WO 9723602	A1	19970703	WO 1996-EP5812	19961219 <--
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				

RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

AU 9713054	A1	19970717	AU 1997-13054	19961219	<--
AU 730222	B2	20010301			
EP 877797	A1	19981118	EP 1996-944641	19961219	<--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
CN 1205737	A	19990120	CN 1996-199175	19961219	<--
BR 9612256	A	19990713	BR 1996-12256	19961219	<--
JP 2000506374	T2	20000530	JP 1997-523329	19961219	<--
AT 199390	E	20010315	AT 1996-203641	19961219	<--
ES 2155166	T3	20010501	ES 1996-203641	19961219	<--
NO 9802810	A	19980821	NO 1998-2810	19980618	<--
US 2002012993	A1	20020131	US 1998-91483	19980619	<--
PRAI US 1995-576483	A	19951221 <--			
WO 1996-EP5812	W	19961219 <--			
WO 1996-EP5818	W	19961219 <--			

AB The invention concerns immortalized cell lines, esp. of keratinocytes and melanocytes derived from normal human skin, as well as a novel serum-free medium for the isolation, growth, and maintenance of these cells. Procedures and compns. are disclosed for producing primary melanocytes and keratinocytes in the absence of serum and without fibroblast nurse cells. Plasmids derived from SV40 virus or papilloma virus 16 were used to immortalize the melanocytes and keratinocytes of this invention. The findings are useful for the improved immunol., pharmacol., photo-, and chemotoxicol. anal. of cutaneous reactions and for the expression of heterologous genes. The cells may be used for studying the inflammation reaction and for skin grafting.

IT **74-79-3**, L-**Arginine**, biological studies
RL: BAC (Biological activity or effector, except adverse); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(immortalized human skin cell lines culture in serum-free medium)

L75 ANSWER 13 OF 35 HCAPLUS COPYRIGHT 2002 ACS
AN 1997:273169 HCAPLUS
DN 126:247763
TI In vitro cytotoxic effects of 4,4'-bipyridyl on normal human keratinocytes
AU Michel-Buono, M.; Buono, J.-P.; **Serre**, G.; Dumont, D.; Bernard, P.
CS Dermatology Unit, Faculty of Medicine, Limoges, Fr.
SO Cell Biol. Toxicol. (**1997**), 13(3), 193-204
CODEN: CBTOE2; ISSN: 0742-2091
PB Kluwer
DT Journal
LA English
AB Recent epidemiol. studies have brought to light a possible link between premalignant or neoplastic skin lesions (Bowen disease, squamous carcinoma) and occupational exposure to 4,4'-bipyridyl (4,4'B), a precursor in the synthesis of paraquat herbicide. The present study used a serum-free cell culture of normal human keratinocytes (NHK) and 2 skin-equiv. models to test the effects of exposure to different concns. of 4,4'B. Cytotoxicity of 4,4'B on NHK was measured by neutral red release assay. Superoxide dismutase (SOD) activity and cell cycle were analyzed in exposed and nonexposed NHK cultures. Histol. and immunohistol. tests enabled evaluation of differentiation and proliferation effects in reconstructed skin models. Results showed that significant cytotoxicity occurred after 5-11 days' exposure to 4,4'B concns. of 10-6-10-3 mol/L (IC50 between 10-3 and 10-4 mol/L 4,4'B after 11 days). Parallel modifications of SOD activity were recorded. Histol. and immunohistol. anal. revealed dose-related 4,4'B effects in reconstructed skin models. This involved abnormal terminal differentiation, connected with **filaggrin** expression, obsd. in skin models exposed to 10-7 and 10-6 mol/L 4,4'B. However, no modification of cell cycle or dysplasia was detected as a result of exposure to 4,4'B. Thus, 4,4'B appears to be cytotoxic for NHK, but as an isolated contaminant, and is unable to induce

keratinocyte dysplasia in vitro. These preliminary results do not exclude a cocarcinogenic action of 4,4'B (with UVB, for example).

L75 ANSWER 14 OF 35 HCAPLUS COPYRIGHT 2002 ACS
AN 1997:243298 HCAPLUS
DN 126:276253
TI Normal human epidermal keratinocytes express in vitro specific molecular forms of (Pro) **filaggrin** recognized by **rheumatoid arthritis**-associated **antifilaggrin autoantibodies**
AU **Girbal-Neuhauser, Elisabeth**; Montezin, Martine; Croute, Francoise; **Sebbag, Mireille**; **Simon, Michel**; Durieux, Jean-Jacques; **Serre, Guy**
CS Department of Biology and Pathology of the Cell, Toulouse-Purpan School of Medicine, INSERM CJF 96-02, IFR 30, University of Toulouse III, Toulouse, Fr.
SO Mol. Med. (N. Y.) (**1997**), 3(2), 145-156
CODEN: MOMEF3; ISSN: 1076-1551
PB Springer
DT Journal
LA English
AB The so-called antikeratin **antibodies** and the antiperinuclear factor are the most specific serol. markers of **rheumatoid arthritis** (RA). They were recently shown to be largely the same **autoantibodies** and to recognize human epidermal **filaggrins** and **profilaggrin**-related proteins of buccal epithelial cells [collectively referred to as (pro)**filaggrin**]. To further characterize the target antigens, the authors investigated their expression by normal human epidermal keratinocytes cultured in differentiating conditions, using immunofluorescence and immunoblotting with RA sera and 3 different monoclonal **antibodies** to (pro) **filaggrin**. On the cornified, stratified epithelial sheets obtained in vitro, RA sera with anti-(pro)**filaggrin** **autoantibodies** (AFA) produced granular staining of the stratum granulosum and diffuse staining of the stratum corneum. The antigens recognized by RA sera strictly colocalized with (pro)**filaggrin** in keratohyalin granules. Following sequential extn. of the proteins from the epithelial sheets, the RA sera and the 3 monoclonal **antibodies** to (pro)**filaggrin**, recognized a series of low-salt-sol. mols., including a neutral/acidic isoform of **filaggrin** and several proteins with sizes and pI intermediates between this isoform and **profilaggrin**. They also recognized urea-sol. high-mol.-wt. **profilaggrin**-related mols. Thus, in vitro epidermal keratinocytes express various mol. forms of (pro)**filaggrin** that bear epitopes targeted by AFA of RA sera, and some of these are absent from epidermis. Moreover, these epitopes, which are present on the keratohyalin granules of buccal epithelial cells but not on those of epidermal cells, are present on the granules of the cultured keratinocytes. This work completes the mol. characterization of the proteins targeted by AFA.

L75 ANSWER 15 OF 35 HCAPLUS COPYRIGHT 2002 ACS
AN 1997:25422 HCAPLUS
DN 126:57796
TI Detection of several families of deiminated proteins derived from **filaggrin** and keratins in guinea pig skin
AU Kan, Shuhei; Asaga, Hiroaki; Senshu, Tatsuo
CS Department Cell Chemistry, Tokyo Metropolitan Institute Gerontology, Tokyo, 173, Japan
SO Zool. Sci. (**1996**), 13(5), 673-678
CODEN: ZOSCEX; ISSN: 0289-0003
PB Zoological Society of Japan
DT Journal
LA English
AB Structural proteins in the mammalian epidermis contain **citrulline** residues generated by enzymic deimination of **arginine** residues. We analyzed deiminated proteins solubilized from sequentially stripped

layers of guinea pig epidermis. Deiminated proteins were localized in the granular and cornified layers. Those in the inner layer enriched with granular cells were resolved into numerous components by two-dimensional gel electrophoresis. An arc-shaped high-mol.-wt. smear and two series of charged isomers among them coincided with **filaggrin** immunoreactivity. Several groups of **filaggrin**-neg. spots appeared to be generated by further deimination and proteolysis of these **filaggrins**. Deiminated protein spots co-migrating with type II and type I keratins were also detected. Deiminated **filaggrins** and their further processed derivs. disappeared in the outer layer, while deiminated keratins persisted. These data suggested that **filaggrin** as well as **profilaggrin** were deiminated during the posttranslational processing in guinea pig skin, and that some keratins were deiminated preferentially during the cornification of epidermis. Possible biol. significance of protein deimination in guinea pig skin was discussed in comparison with our recent finding on deiminated proteins in rat skin.

L75 ANSWER 16 OF 35 HCAPLUS COPYRIGHT 2002 ACS
AN 1996:732727 HCAPLUS
DN 126:86359
TI Protein unfolding by peptidylarginine deiminase. Substrate specificity and structural relationships of the natural substrates trichohyalin and **filaggrin**
AU Tarcsa, Edit; Marekov, Lyuben N.; Mei, Giampiero; Melino, Gerry; Lee, Seung-Chul; Steinert, Peter M.
CS Lab. Skin Biol., Natl. Inst. Health, Bethesda, MD, 20892, USA
SO J. Biol. Chem. (**1996**), 271(48), 30709-30716
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB Peptidylarginine deiminases, which are commonly found in mammalian cells, catalyze the deimination of protein-bound **arginine** residues to **citrullines**. However, very little is known about their substrate requirements and the significance or consequences of this post-synthetic modification. We have explored this reaction in vitro with two known substrates **filaggrin** and trichohyalin. First, the degree and rate of modification of **arginines** to **citrullines** directly correlates with the structural order of the substrate. In **filaggrin**, which has little structural order, the reaction proceeded rapidly to >95% completion. However, in the highly .alpha.-helical protein trichohyalin, the reaction proceeded slowly to about 25% and could be forced to a max. of about 65%. Second, the rate and degree of modification depends on the sequence location of the target **arginines**. Third, we show by gel electrophoresis, CD, and fluorescence spectroscopy that the reaction interferes with organized protein structure: the net formation of .gtoreq.10% **citrulline** results in protein denaturation. Cyanate modification of the lysines in model .alpha.-helix-rich proteins to **homocitrullines** also results in loss of organized structure. These data suggest that the ureido group on the **citrulline** formed by the peptidylarginine deiminase enzyme modification functions to unfold proteins due to decrease in net charge, loss of potential ionic bonds, and interference with H bonds.

L75 ANSWER 17 OF 35 HCAPLUS COPYRIGHT 2002 ACS
AN 1996:521964 HCAPLUS
DN 125:164164
TI Preferential deimination of keratin K1 and **filaggrin** during the terminal differentiation of human epidermis
AU Senshu, Tatsuo; Kan, Shuhei; Ogawa, Hideoki; Manabe, Motomu; Asaga, Hiroaki
CS Dep. Cell Chem., Tokyo Metropolitan Inst. Gerontology, Tokyo, 173, Japan
SO Biochem. Biophys. Res. Commun. (**1996**), 225(3), 712-719
CODEN: BBRCA9; ISSN: 0006-291X

DT Journal
LA English
AB The upper layers of mammalian epidermis contain **citrulline** -contg. proteins formed by enzymic deimination of **Arg** residues. To study the role of protein deimination in epidermal differentiation, the authors identified deiminated proteins extd. from human epidermis. The major deiminated proteins were identified as partially degraded keratin K1, whereas those from keratin K10 and a highly heterogeneous mixt. of deiminated **filaggrin** isomers were detected as minor components. Deiminated keratins were recovered in a fraction enriched with keratins from the conified layers. The subsequent immunohistochem. study showed that deiminated proteins were localized mainly in the lowermost cornified layer, but not in the granular layer. These data suggest that partially degraded/disulfide-crosslinked keratin K1 was preferentially deiminated during the terminal stages of epidermal differentiation. The authors therefore speculated that the protein deimination may influence the interaction of basic K1 with its acidic partner, K10, pre-existent K5/K14 networks, or the keratin-assocd. protein, **filaggrin**.

L75 ANSWER 18 OF 35 HCAPLUS COPYRIGHT 2002 ACS
AN 1996:439586 HCAPLUS
DN 125:138579
TI Evidence that **filaggrin** is a component of cornified cell envelopes in human plantar epidermis
AU **Simon, Michel**; Haftek, Marek; **Sebbag, Mireille**; Montezin, Martine; **Girbal-Neuhauser, Elisabeth**; Schmitt, Daniel; **Serre, Guy**
CS Dep. Biol. Pathol. Cell, Toulouse-Purpan Sch. Med., Toulouse, 31059, Fr.
SO Biochem. J. (**1996**), 317(1), 173-177
CODEN: BIJOAK; ISSN: 0264-6021
DT Journal
LA English
AB Cornified cell envelope (CE) is generated during the late stages of epidermal differentiation and is made up of proteins covalently linked together by transglutaminases. To det. whether **filaggrin** is a component of this structure in humans, highly purified CE from plantar stratum corneum was analyzed. An immunoelectron microscopy anal. showed specific binding of 4 different anti-(pro)**filaggrin** monoclonal **antibodies** to the surface of the CE, proved previously to be free of noncovalently linked proteins. Moreover, the anti-**filaggrin** activity of one of the **antibodies** was absorbed by preincubation with the plantar CE, as detd. by ELISA. Convincingly, fragments of CE produced by proteolytic digestion of the structures were stained by this **antibody** on immunoblots. These data provide direct evidence that **filaggrin** is a component of CE purified from human plantar stratum corneum. Crosslinking between CE and the **filaggrin**-contg. fibrous matrix may enhance the structural cohesion of the corneocytes and thus the resistance of the stratum corneum.

L75 ANSWER 19 OF 35 HCAPLUS COPYRIGHT 2002 ACS
AN 1996:258391 HCAPLUS
DN 124:339937
TI Characterization of an immortalized cell line from a patient with epidermolytic hyperkeratosis
AU Chipev, Constantin C.; Steinert, Peter M.; Woodworth, Craig D.
CS National Institute Arthritis, National Institutes Health, Bethesda, MD, 20892-2755, USA
SO J. Invest. Dermatol. (**1996**), 106(3), 385-90
CODEN: JIDEAE; ISSN: 0022-202X
DT Journal
LA English
AB The most frequent mutation that causes the autosomal dominant skin disease epidermolytic hyperkeratosis (EHK) is an **arginine** to histidine substitution at position 10 in the 1A segment of the rod domain of keratin 10. As an initial step toward developing a strategy for treating EHK, a cell line, EH18-1, was established after keratinocytes derived from an EHK

patient with this mutation were immortalized by a recombinant retrovirus encoding the E6 and E7 genes of human papillomavirus type 18. EH18-1 cells synthesize considerable amts. of keratin 10 mRNA and protein when maintained in either submerged cultures or in organotypic cultures. When grown in organotypic culture, EH18-1 cells form multiple layers and express keratin 10 and **filaggrin** predominantly in the upper layers. Thus, the EH18-1 cell line exhibits several morphol. and biochem. markers of terminal epidermal differentiation. A semiquant. reverse transcriptase polymerase chain reaction assay for keratin 10 mRNA was developed to distinguish between expression of the normal and the mutant alleles.

L75 ANSWER 20 OF 35 HCAPLUS COPYRIGHT 2002 ACS
AN 1995:932546 HCAPLUS
DN 124:6691
TI Monoclonal **antibodies** to human epidermal **filaggrin**, some not recognizing **profilaggrin**
AU **Simon, Michel**; **Sebbag, Mireille**; Haftek, Marek; **Vincent, Christian**; **Girbal-Neuhauser, Elisabeth**; Rakotoarivony, Joel; Somme, Gerard; Schmitt, Daniel; **Serre, Guy**
CS Toulouse-Purpan School Medicine, University Toulouse III, Toulouse, 31059, Fr.
SO J. Invest. Dermatol. (**1995**), 105(3), 432-7
CODEN: JIDEAE; ISSN: 0022-202X
DT Journal
LA English
AB To improve understanding of human **profilaggrin** processing to **filaggrin**, we produced seven monoclonal **antibodies** against epidermal **filaggrin** (AHF1-7). They were characterized on human epidermis by indirect immunofluorescence, immunogold labeling, and immunoblotting and found to be directed against seven different epitopes of (pro)**filaggrin**. AHF1-5 labeled the keratohyalin granules and the fibrous matrix of the lower corneocytes, and recognized **filaggrin** and **profilaggrin**. AHF6 also labeled the keratohyalin granules and the corneocyte matrix, but only recognized **filaggrin**. In addn. to this reactivity within the upper epidermis, AHF4-6 stained the cytoplasm of the basal cells, and cross-reactivity of AHF5 and AHF6 with cytokeratin K14 was revealed on immunoblots. It is interesting that AHF7 recognized **filaggrin**, but not **profilaggrin**, and labeled only the corneocyte matrix and not the keratohyalin granules. This indicates that **filaggrin** and cytokeratins share several antigenic determinants and that **filaggrin** bears at least one epitope absent from its precursor. The original series of monoclonal **antibodies** described here appears to be a powerful tool for studying human **profilaggrin** processing in normal conditions and in the keratinization disorders in which processing is altered.

#11

L75 ANSWER 21 OF 35 HCAPLUS COPYRIGHT 2002 ACS
AN 1995:790254 HCAPLUS
DN 123:253672
TI The antiperinuclear factor and antikeratin **antibody** systems
AU Youinou, Pierre; **Serre, Guy**
CS Medical School Hospital, Brest University, Brest, Fr.
SO Int. Arch. Allergy Immunol. (**1995**), Volume Date 1995, 107(4), 508-18
CODEN: IAAIEG; ISSN: 1018-2438
DT Journal; General Review
LA English
AB A review with 60 refs. Antiperinuclear factor (APF) and antikeratin **antibody** (AKA) have long been known to be assocd. with **rheumatoid arthritis**. Human buccal mucosa epithelial cells have hitherto been required as the substrate in the APF test, while AKAs are detected on rat esophagus sections, using an indirect immunofluorescence technique. These two **autoantibodies** proved to be interrelated. Cytoplasmic inclusions in buccal cells have

presumptively been termed keratohyalin granules and the APF target antigen colocalizes exactly with that of **antiprofilaggrin antibody** within the perinuclear organelles. The latter protein has convincingly been identified as the genuine specificity of the so-called AKA.

L75 ANSWER 22 OF 35 HCAPLUS COPYRIGHT 2002 ACS
AN 1995:745614 HCAPLUS
DN 123:164574
TI Detection of deiminated proteins in rat skin: probing with a monospecific **antibody** after modification of **citrulline** residues
AU Senshu, Tatsuo; Akiyama, Kyoichi; Kan, Shuhei; Asaga, Hiroaki; Ishigami, Akihito; Manabe, Motomu
CS Dep. of Cell Chemistry, Tokyo Metropolitan Inst. of Gerontology, Tokyo, Japan
SO J. Invest. Dermatol. (**1995**), 105(2), 163-9
CODEN: JIDEAE; ISSN: 0022-202X
DT Journal
LA English
AB The authors performed a systematic study on deiminated proteins present in rat epidermis. Proteins extd. from various epidermal samples were resolved by either one- or two-dimensional gel electrophoresis and Western blotted to nitrocellulose membranes. Deiminated proteins were detected by modification of **citrulline** residues followed by probing with an anti-modified **citrulline** monospecific **antibody**. The cornified layer of adult plantar skin gave multiple series of isoelec. variants, most of which were differentially deiminated type Ii keratins (60 kDa, and 67 kDa or above). The whole epidermis of 5-day-old rat back skin showed isoelec. variants of 60-kDa keratin as major deiminated components, and deiminated 55-kDa keratin and deiminated **filaggrin** as minor spots. In addn., the authors found highly deiminated proteins (200-220 kDa) thought to be derived from trichohyalin. The immunoreactivity of deiminated proteins was mainly localized in the granular and cornified layers of epidermis. Co-localization of deiminated **filaggrin** and keratins in the granular layer suggests the possible role of protein deimination during the terminal stage of epidermal differentiation.
IT **372-75-8**, **L-Citrulline**
RL: NUU (Other use, unclassified); USES (Uses)
(detection of deiminated proteins in rat skin: probing with a monospecific **antibody** after modification of **citrulline** residues)

L75 ANSWER 23 OF 35 HCAPLUS COPYRIGHT 2002 ACS
AN 1995:609921 HCAPLUS
DN 123:31150
TI The antiperinuclear factor and the so-called antikeratin **antibodies** are the same **rheumatoid arthritis** -specific **autoantibodies**
AU **Sebbag, Mireille; Simon, Michel; Vincent, Christian**; Masson-Bessiere, Christine; **Girbal, Elisabeth**; Durieux, Jean-Jacques; **Serre, Guy**
CS Dep. Biol. and Pathology Cell, Univ. Toulouse III, Toulouse, 31059, Fr.
SO J. Clin. Invest. (**1995**), 95(6), 2672-9
CODEN: JCINAO; ISSN: 0021-9738
DT Journal
LA English
AB The so-called antikeratin **antibodies** (AKA) and the antiperinuclear factor (APF) are the most specific serol. markers of RA. Using indirect immunofluorescence, AKA label the stratum corneum of various cornified epithelia and APF the keratohyalin granules of human buccal mucosa epithelium. The authors recently demonstrated that AKA recognize human epidermal **filaggrin**. Here, the authors report the identification of the major APF antigen as a diffuse protein band of 200-400 kDa. This protein is seen to be closely related to human epidermal (pro)**filaggrin** since it was recognized by 4

antifilaggrin mAbs specific for different epitopes, and since the APF titers of RA sera were correlated to their AKA titers and to their immunoblotting reactivities to **filaggrin**. Immunoabsorption of RA sera on purified epidermal **filaggrin** abolished their reactivities to the granules of buccal epithelial cells and to the 200-400 kDa antigen. Moreover, **antifilaggrin autoantibodies**, i.e., AKA, affinity purified from RA sera, were shown to immunodetect the 200-400 kDa antigen and to stain these granules. Thus, AKA and APF are largely the same **autoantibodies**. They recognized human epidermal **filaggrin** and (pro)**filaggrin**-related proteins of buccal epithelial cells. Identification of the epitopes recognized by these **autoantibodies**, which the authors propose to name **antifilaggrin autoantibodies**, will certainly open new paths of research into the pathophysiol. of RA.

L75 ANSWER 24 OF 35 HCAPLUS COPYRIGHT 2002 ACS
AN 1995:550480 HCAPLUS
DN 123:28369
TI Rat epidermal cathepsin B: purification and characterization of proteolytic properties toward **filaggrin** and synthetic substrates
AU Kawada, Akira; hara, Kenji; Morimoto, Koukichi; Hiruma, Masataro; Ishibashi, Akira
CS Department of Dermatology, National Defense Medical College, Saitama, 359, Japan
SO Int. J. Biochem. Cell Biol. (**1995**), 27(2), 175-83
CODEN: IJBBFU; ISSN: 1357-2725
DT Journal
LA English
AB The aim of this study was to purify epidermal cathepsin B from rat skin and investigate its proteolytic activities on **filaggrin** and several synthetic substrates. The mol. wt. of purified monomeric cathespin B was estd. to be 30 kDa by SDS-polyacrylamide gel electrophoresis. The amino acid compn., similar to that of liver cathepsin B, indicated the enzyme to be an acidic protease. The enzyme had strong hydrolytic activity toward N-benzyloxycarbonyl-L-**arginyl**-L-**arginine**-7-amido-4-methylcoumarin (Z-**Arg-Arg**-MCA) (152 mU/mg) and N-benzyloxycarbonyl-L-phenylalanyl-L-**arginine**-7-amido-4-methylcoumarin (424 mU/mg), but had no proteolytic activity toward L-**arginine**-7-amido-4-methylcoumarin. The Km value for Z-**Arg-Arg**-MCA was 0.34 mM and pH optimum was 5.5. Cathespin B degraded rat epidermal **filaggrin** into small fragments at pH 4.0 and 5.5, and was inhibited by a specific cysteine proteinase inhibitor, N-[N-(L-3-trans-carboxyoxirane-2-carbonyl)-L-leucyl]-agmatin. This study demonstrated that flaggrin was susceptible to degrdn. by cathespin B. Such an action may have relevance to skin differentiation in which acid proteases are through to participate.

L75 ANSWER 25 OF 35 HCAPLUS COPYRIGHT 2002 ACS
AN 1994:517737 HCAPLUS
DN 121:117737
TI Peptide compositions for use in pharmaceutical, cosmetic, and biotechnological applications
IN Quelle, Gerhard
PA Germany
SO Ger. Offen., 24 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 4244415	A1	19940630	DE 1992-4244415	19921229 <--

AB Peptides and peptide-amino acid mixts. obtained by partial hydrolysis of collagen, gelatin, elastin, keratin, or connective tissue, or synthetic mixts. with similar compns., are useful (a) in biotechnol. as additives to

serum-free or serum-depleted cell culture nutrient media, (b) in medicine as wound healing promoters, immunostimulants, and stimulants of erythropoietin formation, and (c) in cosmetics as skin conditioners, anti-aging factors, and radical scavengers. The peptides contain the sequences Gly-His-Lys and/or Gly-Asp-Ser, and may be complexed with trace metals. The compns. may also contain carbohydrates, lipids, phospholipids, glycolipids, nucleic acids, enzymes, cytokines, etc. to enhance the activity of the peptides, as well as extraneous peptides to diminish adsorption of the active peptides on glass or plastic surfaces. Thus, 1 kg denatured collagen was hydrolyzed with 1N HCl at 100.degree. for 3 h, neutralized, desalted, and dild. to 20 L. This hydrolyzate caused a 60% stimulation of metab. by rat liver mitochondria. The hydrolyzate was stabilized with a mixt. of Na ascorbate 1.0, mannitol 20.0, glycerol 50.0, Na lactate 20.0, soybean peptides 1.0, Me hydroxybenzoate Na salt 1.0,and phenonip 2.0 g/L.

L75 ANSWER 26 OF 35 HCAPLUS COPYRIGHT 2002 ACS
AN 1994:132136 HCAPLUS
DN 120:132136
TI Characterization of the rat esophagus epithelium antigens defined by the so-called 'antikeratin **antibodies**', specific for **rheumatoid arthritis**
AU **Girbal, Elisabeth**; **Sebbag, Mireille**; Gomes-Daudrix, Veronique; **Simon, Michel**; **Vincent, Christian**; **Serre, Guy**
CS Purpan Med. Sch., Univ. Toulouse III, Toulouse, 31059, Fr.
SO Ann. Rheum. Dis. (**1993**), 52(10), 749-57
CODEN: ARDIAO; ISSN: 0003-4967
DT Journal
LA English
AB An attempt was made to characterize the antigens recognized by serum IgG **antibodies** directed to the stratum corneum of rat esophagus epithelium, the so-called 'antikeratin **antibodies**', which were shown to be highly specific for **rheumatoid arthritis** (RA) and thus to have an actual diagnostic value. Immunoblotting was performed with RA serum samples on different exts. of rat esophagus epithelium sepd. by various monodimensional and two dimensional electrophoreses. Three low-salt-sol. antigens sensitive to proteinase K and, therefore, of protein nature were identified. Two proteins, with apparent mol. masses of 210 and 90-120 kilodaltons, shared isoelec. points ranging from 5.8 to 8.5; the third protein exhibited isoelec. points from 4.5 to 7.2 while its mol. mass ranged from 60 to 130 kilodaltons. Immunoadsorption of RA serum samples onto cytokeratins extd. from the stratum corneum of rat esophagus epithelium did not change their immunoreactivity towards the three antigenic proteins. Widely used deglycosylation and dephosphorylation methods failed to modify either the electrophoretic migration of the proteins or their immunoreactivity with RA serum samples. The so-called 'antikeratin **antibodies**' do not react with cytokeratins. They specifically recognize three late epithelial differentiation proteins that have not been previously described. These proteins may be related to (pro)**filaggrin**.

L75 ANSWER 27 OF 35 HCAPLUS COPYRIGHT 2002 ACS
AN 1994:48327 HCAPLUS
DN 120:48327
TI Characterization of protease processing sites during conversion of rat **profilaggrin** to **filaggrin**
AU Resing, K. A.; Johnson, R. S.; Walsh, K. A.
CS Dep. Biochem., Univ. Washington, Seattle, WA, 98195, USA
SO Biochemistry (**1993**), 32(38), 10036-45
CODEN: BICHAW; ISSN: 0006-2960
DT Journal
LA English
AB **Profilaggrin** is an intermediate filament-assocd. protein of cornified epithelia. It consists of multiple copies of similar **filaggrin** domains joined by peptide linker regions; during

terminal differentiation of the epidermis, the linker regions are processed away in a regulated manner. In order to characterize the sites of proteolysis in rat **profilaggrin**, tryptic peptides of **filaggrin** and **profilaggrin** were fractionated by reverse-phase HPLC, and the HPLC fractions were analyzed by nebulization-assisted electrospray ionization mass spectrometry. Peptide sequences were confirmed or cor. by tandem mass spectrometry; in several cases, this was achieved by collisional activation of multiply charged precursor ions of peptides exceeding 3 kDa in mass. The tryptic peptides accounted for all of the sequence predicted by a partial cDNA sequence, with the exception of six **arginines** or dipeptides. Although the cDNA sequence predicted eight sites of heterogeneity among the **filaggrin** domains, only one of these was obsd. An addnl. unpredicted site of heterogeneity was also seen. Comparison of the peptides from **filaggrin** with those of **profilaggrin** revealed several peptides unique to **filaggrin**, specifically at the new amino- and carboxyl termini, that result from proteolytic processing of the linker region of **profilaggrin**. Both the amino- and carboxyl-termini were "ragged", suggesting that processing may involve exopeptidase action after an initial endopeptidase cleavage. The av. mass of this mixt. of **filaggrins** was detd. by electrospray mass spectrometry to be 42,452 Da, in reasonable agreement with that predicted from the mass spectrometric anal. of the terminal sequences. The linker peptide of rat **profilaggrin** was found in two forms, which differed only in the phosphorylation state of serine 22.

IT **152143-24-3, Profilaggrin** (rat epidermis phosphoprotein internal fragment ordered gapped protein)
RL: BIOL (Biological study)
(amino acid sequence and proteinase processing sites of and cDNA predicted sequence comparison with, processing mechanism in relation to)

L75 ANSWER 28 OF 35 HCAPLUS COPYRIGHT 2002 ACS
AN 1993:647879 HCAPLUS
DN 119:247879
TI The cytokeratin filament-aggregating protein **filaggrin** is the target of the so called "antikeratin **antibodies**," **autoantibodies** specific for **rheumatoid arthritis**
AU **Simon, Michel**; **Girbal, Elisabeth**; **Sebbag, Mireille**; Gomes-Daudrix, Veronique; **Vincent, Christian**; Salama, Gilles; **Serre, Guy**
CS Toluouse-Purpan Sch. Med., Univ. Toulouse III, Toulouse, Fr.
SO J. Clin. Invest. (**1993**), 92(3), 1387-93
CODEN: JCINAO; ISSN: 0021-9738
DT Journal
LA English
AB In **rheumatoid arthritis** (RA), the high diagnostic value of serum **antibodies** to the stratum corneum of rat esophagus epithelium has been widely reported. These so-called "antikeratin **antibodies**," detected by indirect immunofluorescence, were **autoantibodies** since they also labeled human epidermis. Despite their name, the actual target of these **autoantibodies** was not known. In this study, a 40 kDa protein (designated as 40K), extd. from human epidermis and specifically immunodetected by 75% of RA sera, was purified and identified as a neutral/acidic isoform of basic **filaggrin**, a cytokeratin filament-aggregating protein, by peptide mapping studies, and by the following evidence: (a) mAbs specific for **filaggrin** reacted with the 40K protein; (b) the **autoantibodies**, affinity-purified from RA sera on the 40K protein, immunodetected purified **filaggrin**; (c) the reactivity of RA sera to the 40K protein was abolished after immunoadsorption with purified **filaggrin**; and (d) the 40K protein and **filaggrin** had similar amino acid compns. Furthermore, **autoantibodies** against the 40K protein and the so-called "antikeratin **antibodies**" were shown, by immunoadsorption expts., to be largely the same. The identification of

filaggrin as a RA-specific autoantigen could contribute to the understanding of the pathogenesis of this disease and, ultimately, to the development of methods for preventing the autoimmune response.

L75 ANSWER 29 OF 35 HCAPLUS COPYRIGHT 2002 ACS
AN 1993:619914 HCAPLUS
DN 119:219914
TI The mechanism of interaction of **filaggrin** with intermediate filaments. The ionic zipper hypothesis
AU Mack, James W.; Steven, Alasdair C.; Steinert, Peter M.
CS Skin Biol. Branch, Natl. Inst. Arthritis Musculoskeletal Skin Dis., Bethesda, MD, 20892, USA
SO J. Mol. Biol. (**1993**), 232(1), 50-66
CODEN: JMOBAK; ISSN: 0022-2836
DT Journal
LA English
AB **Filaggrins** of mammalian epidermis represent archetypical examples of intermediate filament-assocd. proteins that can bind large nos. of intermediate filaments in vitro (and keratin filaments in vivo) into macrofibrils. To explore the mechanism of this interaction, the secondary structures of **filaggrins** were analyzed. As much as 80% of mouse and human **filaggrins** consist of multiple repeating elements. The first level consists of a tetrapeptide .beta.-turn motif in which about 35% of the turns are pos. charged and about 10% are neg. charged. At the next level, triplets of this motif form segments 13 to 14 residues in length, which in turn are repeated two to six times into blocks sepd. by short hydrophobic sequences to constitute a complete **filaggrin** mol. Thus, **filaggrins** evolved by frequent duplications of a primordial repeat unit of about 13 to 14 residues with subsequent retention of the conserved .beta.-turn and charge characteristics. To test how these features bind filaments, two approaches were used. Of a series of synthetic peptides, those of 20 to 26 residues (about 2 segments) contg. at least five .beta.-turns with a net charge of +2 (i.e., about 40% of the turns are pos. charged) were as effective as full length **filaggrin** in binding large nos. of both type I/II keratin and type III vimentin/desmin filaments, as judged by electron microscopy. Secondly, macrofibrils formed from unlabeled **filaggrin** and keratin filaments labeled in vivo with [1-13C]glycine or L-[4,4,5,5-2H4]lysine were probed by NMR. The effective isotropy and time scale of mobilities of the glycine-labeled end domains were essentially identical in keratin filaments alone and those bound in macrofibrils, suggesting that **filaggrins** do not bind filaments by way of their end domains. However, the lysine-labeled rod domains of the filaments in macrofibrils were considerably more constrained than in filaments alone. These data support the hypothesis that **filaggrins** bind filaments by way of simple ionic and/or H-bonding interactions between the conserved pos. and neg. charges on the .beta.-turns of **filaggrins** and the conserved distributions of neg. and pos. charges along the packed rod domains of intermediate filaments, as in an ionic zipper.

L75 ANSWER 30 OF 35 HCAPLUS COPYRIGHT 2002 ACS
AN 1993:5600 HCAPLUS
DN 118:5600
TI Antigens recognized by **rheumatoid polyarthritis autoantibodies**, their preparation and applications
IN **Serre, Guy**; Somme, Gerard; **Vincent, Christian**
PA Clonatec S.A., Fr.
SO Eur. Pat. Appl., 38 pp.
CODEN: EPXXDW
DT Patent
LA French
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 511116	A1	19921028	EP 1992-401185	19920424 <--

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, PT, SE

FR 2675805	A1	19921030	FR 1991-4983	19910426	<--
FR 2681600	A1	19930326	FR 1991-11727	19910924	<--
FR 2681600	B1	19950519			
CA 2084876	AA	19921027	CA 1992-2084876	19920424	<--
WO 9219649	A1	19921112	WO 1992-FR371	19920424	<--
W: CA, JP, US					
JP 06502187	T2	19940310	JP 1992-510455	19920424	<--
US 5888833	A	19990330	US 1994-253762	19940603	<--

PRAI FR 1991-4983 19910426 <--
FR 1991-11727 19910924 <--
WO 1992-FR371 19920424 <--
US 1993-958353 19930127 <--

AB Antigens are disclosed which are reactive with **autoantibodies** present in patients with **rheumatoid polyarthritis**. The antigens have immunol. and biochem. properties in common with human **filaggrin** and corresponding to a proteolytic fragment of **profilaggrin**. The antigens are useful for the diagnosis of **rheumatoid polyarthritis** and for purifn. of the **autoantibodies**. The antigens were isolated from human epidermis and from rat esophageal epithelium.

L75 ANSWER 31 OF 35 HCAPLUS COPYRIGHT 2002 ACS
AN 1991:652601 HCAPLUS
DN 115:252601
TI Immunocytochemical evidence for a possible role of cross-linked keratinocyte envelopes in stratum corneum cohesion
AU Haftek, Marek; **Serre, Guy**; Mils, Valerie; Thivolet, Jean
CS Clin. Dermatol., Hop. E. Herriot, Lyon, Fr.
SO J. Histochem. Cytochem. (**1991**), 39(11), 1531-8
CODEN: JHCYAS; ISSN: 0022-1554
DT Journal
LA English
AB Crosslinked cornified envelopes are cell structures specifically synthesized by terminally differentiating keratinocytes. They are composed of proteins deposited at the cell periphery under the plasma membrane, and can be purified from epidermis by physicochem. extns. The resulting keratinocyte shells are highly insol. structures devoid of cytoplasmic components. The rigidity of the stratum corneum cell envelope seems to be one of the essential factors contributing to the phys. resistance of this most superficial epidermal layer. The purified cell envelopes from human plantar horny layer were studied to det. their antigenic compn. and protein distribution. The extn. protocol consisted of four 10-min cycles of boiling in 10 mM Tris-HCl buffer contg. 2% SDS and 1% .beta.-mercaptoethanol. The absence of any extractable proteins persisting in the purified pellets was checked with SDS-PAGE of the sample electroeluates. Indirect immunofluorescence as well as pre- and post-embedding immunogold labeling for electron microscopy revealed the persistence of several keratinocyte antigenic determinants on the purified substrates. The **antibodies** directed against involucrin, keratin 10, desmoplakin I + II, desmoglein (intracellular epitope), intercellular corneodesmosome proteins, and **filaggrin** (a considerably weaker reactivity) labeled the cell envelopes according to the ultrastructural localization pattern characteristic for a given antigen. It is concluded that the cytoskeletal and desmosomal components become embedded in the highly crosslinked cornified envelope structures during the process of keratinocyte terminal differentiation. This underlines the central role of cornified envelopes in the phys. resistance of superficial epidermal layers and indicates a possible importance of junctional proteins in this function.

L75 ANSWER 32 OF 35 HCAPLUS COPYRIGHT 2002 ACS
AN 1991:59881 HCAPLUS
DN 114:59881
TI Effects of aging and xerosis on the amino acid composition of human skin
AU Jacobson, Tony M.; Yuksel, K. Umit; Geesin, Jeffery C.; Gordon, Joel S.;

Lane, Alfred T.; Gracy, Robert W.
CS Texas Coll. Osteopath. Med., Univ. North Texas, Ft. Worth, TX, 76107, USA
SO J. Invest. Dermatol. (**1990**), 95(3), 296-300
CODEN: JIDEAE; ISSN: 0022-202X
DT Journal
LA English
AB Amino acid compns. of skin samples from young and old subjects and from age-matched donors with dry skin syndrome (xerosis) were examd. The amino acid contents of the free amino acid (FAA) fraction, sol. hydrolyzate (SH) fraction, and whole cell hydrolyzate (WCH) were detd. The greater differences were obsd. between the FAA compns. of the young and old normal subjects. Xerosis did not appear to affect the amino acid compns. of samples from young subjects as much as old subjects. Overall, the effect of aging on the amino acid contents was more pronounced than the effect of xerosis. The amino acid compns. of the FAA showed a high degree of similarity to **filaggrin**, whereas the WCH showed a similarity to keratin.
IT **74-79-3**, **Arginine**, biological studies
RL: BIOL (Biological study)
(of skin, aging and xerosis effect on, of humans)

L75 ANSWER 33 OF 35 HCAPLUS COPYRIGHT 2002 ACS
AN 1986:221054 HCAPLUS
DN 104:221054
TI Isolation and characterization of a 30 kDa membrane glycoprotein from human stratum corneum
AU Chen, Shu Jen; Rajaraman, Srinivasan; Miller, Joanne; Kalmaz, Gulgun D.; Brysk, Miriam M.
CS Dep. Dermatol., Univ. Texas, Galveston, TX, 77550, USA
SO Biochim. Biophys. Acta (**1986**), 881(3), 375-82
CODEN: BBACAQ; ISSN: 0006-3002
DT Journal
LA English
AB By using iodinated Con A in conjunction with gel electrophoresis, a 30-kilodalton (kDa) glycoprotein was identified in the stratum corneum of human skin. This glycoprotein was isolated by extn. in nonionic detergent, affinity chromatog., and preparative gel electrophoresis. It binds to Con A but not to 3 other lectins. The purified glycoprotein migrates at 30 kDa whether or not reducing agents are present. It is rich in histidine and lysine, but lacks **arginine**, proline, tyrosine, and methionine. It is clearly distinct from **filaggrin**. A monospecific polyclonal **antibody** was prepd. to this glycoprotein and used to localize the protein by immunohistochem. exclusively to the cell membrane of corneocytes. The glycoprotein may play a role in the cohesion and desquamation of corneocytes.

L75 ANSWER 34 OF 35 HCAPLUS COPYRIGHT 2002 ACS
AN 1984:20842 HCAPLUS
DN 100:20842
TI Histidine-rich proteins (**filaggrins**): structural and functional heterogeneity during epidermal differentiation
AU Harding, Clive R.; Scott, Ian R.
CS Environ. Saf. Lab., Sharnbrook/Bedford, MK44 1LQ, UK
SO J. Mol. Biol. (**1983**), 170(3), 651-73
CODEN: JMOBAK; ISSN: 0022-2836
DT Journal
LA English
AB The urea-sol. protein profiles of guinea pig, rat, mouse, and human epidermis were compared by nonequil. pH gradient/SDS 2-dimensional gel electrophoresis. The **filaggrins** were identified by their characteristic specificity and kinetics of labeling with [3H]histidine and 32PO43-, and by their ability in vitro to aggregate keratin filaments specifically into bundles. In all species, the phosphorylated **filaggrin** precursor, **profilaggrin**, is resolved as a single or double band with an apparent mol. wt. >300,000 and a neutral or slightly acidic isoelec. point. In striking contrast, the strongly basic

filaggrins produced from similar **profilaggrins** form mol. wt. families that are clearly species specific. In rat and man, there is a single, principal mol. wt. form of **filaggrin** (relative mol. wts. 45,000 and 38,000, resp.), whereas mouse and guinea pig have heterogeneous families, including high-mol.-wt. (>200,000) variants. Even **filaggrins** of a particular mol. wt. are not homogeneous, but consist of a no. of isoelec. variants, some of which are considerably less basic than the bulk of the **filaggrins**. Incorporation studies using [3H]**arginine** and 32PO43- indicate that the isoelec. variance is not due to residual phosphate following **profilaggrin** breakdown, but rather to a conversion of basic **arginine** residues into neutral **citrulline** residues. **Filaggrins** of all the mol. wts. from all the species studied share the ability to aggregate keratin filaments into large, insol. macrofibrils. However, the more acidic isoelec. variants have lower affinities for keratin, particularly in man and guinea pig where the most acidic **filaggrins** have completely lost the ability to aggregate keratins. The possibility that a loss of keratin binding ability, resulting in a loosening of the keratin fiber/**filaggrin** matrix, is necessary before the normal complete proteolysis of the **filaggrins** can occur is discussed.

IT **74-79-3**, biological studies
RL: BIOL (Biological study)
(**citrulline** formation from, in **filaggrin** of human and other mammals, multiple and species-specific **filaggrin** forms in relation to)

IT **372-75-8**
RL: FORM (Formation, nonpreparative)
(formation of, from **arginine** in **filaggrins** of humans and other mammals, multiple and species-specific forms in relation to)

L75 ANSWER 35 OF 35 HCAPLUS COPYRIGHT 2002 ACS
AN 1983:175170 HCAPLUS
DN 98:175170
TI The characterization of human epidermal **filaggrin**. A histidine-rich, keratin filament-aggregating protein
AU Lynley, Alexis M.; Dale, Beverly A.
CS Dep. Med., Univ. Washington, Seattle, WA, 98195, USA
SO Biochim. Biophys. Acta (**1983**), 744(1), 28-35
CODEN: BBACAQ; ISSN: 0006-3002
DT Journal
LA English
AB **Filaggrin**, a histidine-rich, cationic protein that aggregates with keratin filaments in vitro and may function as the keratin matrix protein in the terminally differentiated cells of the epidermis, was identified in human skin, isolated, and characterized by biochem. and immunol. techniques. Indirect immunofluorescence of human skin using antiserum to rat **filaggrin** gave pos. immunofluorescence of keratohyalin granules and the stratum corneum. This indicated the presence of a human **filaggrin** in the epidermis in a localization similar to that of the rodent. The protein was isolated from human epidermis and purified by ion-exchange chromatog. and preparative gel electrophoresis. The purified protein cross-reacts with **antibody** to rat **filaggrin** and migrates as a doublet of mol. wt. .apprx.35,000 on SDS-polyacrylamide gels. It is relatively rich in polar amino acids such as histidine, **arginine**, serine, and glycine, but is poor in nonpolar amino acids. Unlike rodent **filaggrin**, the human protein contains ornithine. This protein aggregates with human keratin filaments, forming compact macrofibrils in a manner analogous to that of rodent **filaggrin**.

=> d 176 bib abs hitrn retable tot

L76 ANSWER 1 OF 7 HCAPLUS COPYRIGHT 2002 ACS
AN 2002:1017 HCAPLUS

TI Specific presence of intracellular **citrullinated** proteins in **rheumatoid arthritis** synovium: Relevance to **antifilaggrin autoantibodies**

AU Baeten, Dominique; Peene, Isabelle; Union, Ann; Meheus, Lydie; **Sebbag, Mireille; Serre, Guy**; Veys, Eric M.; De Keyser, Filip

CS Ghent University, Ghent, Belg.

SO Arthritis & Rheumatism (2001), 44(10), 2255-2262
CODEN: ARHEAW; ISSN: 0004-3591

PB Wiley-Liss, Inc.

DT Journal

LA English

AB To investigate the presence of **citrullinated** proteins in the synovial membrane of patients with **rheumatoid arthritis** (RA) and controls, and to analyze a possible relationship with **antifilaggrin auto-antibody** (AFA) reactivity.
Synovial biopsy samples were obtained from 88 consecutive patients undergoing needle arthroscopy for knee synovitis assocd. with RA (n = 36), spondylarthropathy (n = 35), **osteoarthritis** (n = 9), or other diagnoses (n = 8). Tissue sections were stained with 2 different **anticitrulline** polyclonal **antibodies** and an **antifilaggrin** monoclonal **antibody** (mAb). The phenotype of **citrulline**-pos. cells and the colocalization with affinity-purified AFA were investigated by double immunofluorescence on frozen sections. Studies with the first **antibody** showed that **citrulline** is expressed intracellularly in the lining and sublining layers of RA synovial tissue. Staining with the second **antibody**, monospecific for proteins contg. modified **citrulline**, and with anti-inducible nitric oxide synthetase confirmed the presence of **citrullinated** proteins rather than free **citrulline** in the synovium. **Citrulline**-pos. cells were detected in 50% of the RA patients (18 of 36) but in none of the controls (0 of 52). The **anticitrulline** reactivity colocalized with affinity-purified AFA reactivity, although stainings with the **antifilaggrin** mAb indicated the absence of **filaggrin** in the synovium. Intracellular **citrullinated** proteins, which are not recognized by an **antifilaggrin** mAb, are expressed in RA but not in control synovium. The high specificity of this finding and the colocalization with AFA reactivity boost the interest in **citrullinated** proteins as possible triggers of autoimmune responses in RA. Moreover, this is the first description of a specific histol. marker for RA synovium.

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Altman, R	1986	29	1039	Arthritis Rheum	MEDLINE
Arnett, F	1988	31	315	Arthritis Rheum	MEDLINE
Asaga, H	1998	243	641	Biochem Biophys Res	HCAPLUS
Baeten, D	2000	59	945	Ann Rheum Dis	MEDLINE
Baeten, D	1999	18	434	Clin Rheumatol	MEDLINE
Blass, S	1998	57	220	Ann Rheum Dis	HCAPLUS
Brahms, H	2000	275	17122	J Biol Chem	HCAPLUS
Despres, N	1994	21	1027	J Rheumatol	HCAPLUS
Dougados, M	1991	34	1218	Arthritis Rheum	MEDLINE
Girbal, E	1993	52	749	Ann Rheum Dis	HCAPLUS
Girbal-Neuhauser, E	1999	162	585	J Immunol	HCAPLUS
Goldbach-Mansky, R	2000	2	236	Arthritis Res	HCAPLUS
Guerassimov, A	1998	41	1019	Arthritis Rheum	HCAPLUS
Hoet, R	1991	50	611	Ann Rheum Dis	MEDLINE
Janssens, X	1988	15	1346	J Rheumatol	MEDLINE
Kraan, M	1999	38	1074	Rheumatology (Oxford	MEDLINE
Masson-Bessiere, C	2000	119	544	Clin Exp Immunol	HCAPLUS
Masson-Bessiere, C	2001	166	4177	J Immunol	HCAPLUS
Pozza, M	2000	27	1121	J Rheumatol	HCAPLUS
Schellekens, G	1998	101	273	J Clin Invest	HCAPLUS

Sebbag, M	1995	95	2672	J Clin Invest	HCAPLUS
Senshu, T	1992	203	94	Anal Biochem	HCAPLUS
Senshu, T	1996	225	712	Biochem Biophys Res	HCAPLUS
Senshu, T	1995	105	163	J Invest Dermatol	HCAPLUS
Simon, M	1995	100	90	Clin Exp Immunol	MEDLINE
Simon, M	1993	92	1387	J Clin Invest	HCAPLUS
Utz, P	1998	41	1152	Arthritis Rheum	HCAPLUS
Verheijden, G	1997	40	1115	Arthritis Rheum	HCAPLUS
Vincent, C	1999	58	42	Ann Rheum Dis	MEDLINE
Vincent, C	1998	25	838	J Rheumatol	HCAPLUS
Williams, D	1994		9.1	Rheumatology, 1st ed	

L76 ANSWER 2 OF 7 HCAPLUS COPYRIGHT 2002 ACS
AN 2001:689574 HCAPLUS
TI Performance of two ELISAs for **antifilaggrin autoantibodies**, using either affinity purified or deiminated recombinant human **filaggrin**, in the diagnosis of **rheumatoid arthritis**
AU Nogueira, L.; **Sebbag, M.**; **Vincent, C.**; **Arnaud, M.**; Fournie, B.; Cantagrel, A.; **Jolivet, M.**; **Serre, G.**
CS Department of Biology and Pathology of the Cell, Institut National de la Sante et de la Recherche Medicale, Preval, Fr.
SO Ann. Rheum. Dis. (2001), 60(9), 882-887
CODEN: ARDIAO; ISSN: 0003-4967
PB BMJ Publishing Group
DT Journal
LA English
AB Objective-To develop a standardisable enzyme linked immunosorbent assay (ELISA), using human **filaggrin**, for detection of **antifilaggrin autoantibodies** in **rheumatoid arthritis** (RA). To compare the diagnostic performance of the ELISA with those of ref. tests: "antikeratin **antibodies**" ("AKA"), and **antibodies** to human epidermis **filaggrin** detected by immunoblotting (AhFA-IB). Methods-Two ELISAs were developed using either affinity purified neutralacidic human epidermis **filaggrin** (AhFA-ELISA-pur) or a recombinant human **filaggrin** deiminated in vitro (AhFA-ELISA-rec) as immunosorbent. **Antifilaggrin autoantibodies** were assayed in 714 serum samples from patients with well characterised **rheumatic** diseases, including 241 RA and 473 other **rheumatic** diseases, using the two ELISAs. "AKA" and AhFA-IB tests were carried out in the same series of patients. The diagnostic performance of the four tests was compared and their relationships analyzed. Results-The titers of "AKA", AhFA-IB, and the AhFA-ELISAs correlated strongly with each other. The diagnostic sensitivity of the AhFA-ELISA-rec, which was better than that of AhFA-ELISA-pur, was 0.52 for a specificity of 0.95. This performance was similar to those of "AKA" or AhFA-IB. However, combining AhFA-ELISA-rec with AhFA-IB led to a diagnostic sensitivity of 0.55 for a specificity of 0.99. Conclusion-A simple and easily standardisable ELISA for detection of **antifilaggrin autoantibodies** was developed and validated on a large series of patients using a **citrullinated** recombinant human **filaggrin**. The diagnostic performance of the test was similar to that of the "AKA" and AhFA-IB. Nevertheless, combining the AhFA-ELISA-rec with one of the other tests clearly enhanced the performance.

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Aho, K	1993	20	1278	J Rheumatol	MEDLINE
Aho, K	1999	28	113	Scand J Rheumatol	MEDLINE
Arnett, F	1988	31	315	Arthritis Rheum	MEDLINE
Girbal, E	1993	52	749	Ann Rheum Dis	HCAPLUS
Girbal-Neuhauser, E	1999	162	585	J Immunol	HCAPLUS
Goldbach-Mansky, R	2000	2	236	Arthritis Res	HCAPLUS

Gomes-Daudrix, V	1994	53	735	Ann Rheum Dis	MEDLINE
Harding, C	1983	170	651	J Mol Biol	HCAPLUS
Hoet, R	1992		299	Rheumatoid arthritis	
Kroot, E	2000	43	1831	Arthritis Rheum	HCAPLUS
Kurki, P	1992	35	914	Arthritis Rheum	MEDLINE
Masson-Bessiere, C	2000	119	544	Clin Exp Immunol	HCAPLUS
Masson-Bessiere, C	2001	166	4177	J Immunol	HCAPLUS
Meyer, O	1997	56	682	Ann Rheum Dis	MEDLINE
Munoz-Fernandez, S	1999	26	2572	J Rheumatol	MEDLINE
Nienhuis, R	1964	23	302	Ann Rheum Dis	MEDLINE
Paimela, L	1992	51	743	Ann Rheum Dis	MEDLINE
Palosuo, T	1998	115	294	Int Arch Allergy Imm	HCAPLUS
Schellekens, G	2000	43	155	Arthritis Rheum	HCAPLUS
Schellekens, G	1998	101	273	J Clin Invest	HCAPLUS
Sebbag, M	1995	95	2672	J Clin Invest	HCAPLUS
Simon, M	1993	92	1387	J Clin Invest	HCAPLUS
Simon, M	1995	105	432	J Invest Dermatol	HCAPLUS
van Jaarsveld, C	1999	17	689	Clin Exp Rheumatol	MEDLINE
van der Heide, A	1996	124	699	Ann Intern Med	HCAPLUS
Vincent, C	1989	48	712	Ann Rheum Dis	MEDLINE
Vincent, C	1999	58	42	Ann Rheum Dis	MEDLINE
Vincent, C	1998	25	838	J Rheumatol	HCAPLUS
von Essen, R	1993	22	267	Scand J Rheumatol	MEDLINE
Young, B	1979	2	97	BMJ	HCAPLUS

L76 ANSWER 3 OF 7 HCAPLUS COPYRIGHT 2002 ACS
AN 2001:205541 HCAPLUS
DN 134:352031
TI The major synovial targets of the **rheumatoid arthritis** -specific **antifilaggrin autoantibodies** are deiminated forms of the .alpha.- and .beta.-chains of fibrin
AU Masson-Bessiere, Christine; **Sebbag, Mireille**; **Girbal-Neuhauser, Elisabeth**; Nogueira, Leonor; **Vincent, Christian**; Senshu, Tatsuo; **Serre, Guy**
CS Department of Biology and Pathology of the Cells, Institut National de la Sante et de la Recherche Medicale Contrat Jeune Formation 96-02, Toulouse-Purpan School of Medicine, University Toulouse III (Institut Federatif de Recherche 30, Institut National de la Sante et de la Recherche Medicale-Centre, Toulouse, Fr.
SO Journal of Immunology (2001), 166(6), 4177-4184
CODEN: JOIMA3; ISSN: 0022-1767
PB American Association of Immunologists
DT Journal
LA English
AB IgG anti-**filaggrin autoantibodies** (AFA) are the most specific serol. markers of **rheumatoid arthritis**. In epithelial tissues, they recognize **citrulline**-bearing epitopes present on various mol. forms of (pro)**filaggrin**. Histol. anal. of **rheumatoid** synovial membranes with an Ab to **citrulline** showed labeling of interstitial amorphous deposits and mononuclear cells of various types. Immunochem. anal. of exhaustive sequential exts. of the same tissues showed that they contain several deiminated (**citrulline** contg.) proteins. Among them, two proteins, p64-78 and p55-61, present in urea-DTT and guanidine exts., were shown by immunoblotting to be specifically targeted by AFA. By amino-terminal sequencing the proteins were identified as deiminated forms of the .alpha.- and .beta.-chains of fibrin, resp. Their identity was confirmed using several Abs specific for the A.alpha.- and/or to the B.beta.-chain of fibrin(ogen). Moreover, AFA-pos. **rheumatoid arthritis** (RA) sera and purified AFA were highly reactive to the A.alpha.- and B.beta.-chains of human fibrinogen only after deimination of the mols. by a peptidylarginine deiminase. **Autoantibodies** affinity purified from a pool of RA sera onto deiminated fibrinogen were reactive toward all of the epithelial and synovial targets of AFA. This confirmed that the **autoantibodies** to the deiminated A.alpha.-and B.beta.-chains of fibrinogen, the **autoantibodies** to the synovial

proteins p64-78 and p55-61, and, lastly, AFA, constitute largely overlapping **autoantibody** populations. These results show that deiminated forms of fibrin deposited in the **rheumatoid** synovial membranes are the major target of AFA. They suggest that autoimmunization against deiminated fibrin is a crit. step in RA pathogenesis.

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Arnett, F	1988	31	315	Arthritis Rheum	MEDLINE
Asaga, H	1998	243	641	Biochem Biophys Res	HCAPLUS
Bach, A	1972	31	59	Ann Rheum Dis	
Berthelot, J	1997	56	123	Ann Rheum Dis	MEDLINE
Broek, D	1985	260	555	J Biol Chem	HCAPLUS
Busso, N	1998	102	41	J Clin Invest	HCAPLUS
Clemmensen, I	1983	31	479	Arthritis Rheum	
Dumonde, D	1962	43	373	Br J Exp Pathol	HCAPLUS
Furmaniak-Kazmierczak,	1994	94	472	J Clin Invest	HCAPLUS
Girbal, E	1993	52	749	Ann Rheum Dis	HCAPLUS
Girbal-Neuhauser, E	1999	162	585	J Immunol	HCAPLUS
Gomes-Daudrix, V	1994	53	735	Ann Rheum Dis	MEDLINE
Hantgan, R	1994		277	Hemostasis and Throm	
Inagaki, M	1989	264	18119	J Biol Chem	HCAPLUS
Korganow, A		10	451	Immunity	HCAPLUS
Kurki, P	1992	35	914	Arthritis Rheum	MEDLINE
Kurokawa, T	1987	101	1361	J Biochem	HCAPLUS
Lau, C	1993	52	643	Ann Rheum Dis	MEDLINE
Masson-Bessiere, C	2000	119	544	Clin Exp Immunol	HCAPLUS
Matsumoto, I	1999	286	1732	Science	HCAPLUS
Meyer, O	1997	56	682	Ann Rheum Dis	MEDLINE
Mizoguchi, M	1998	46	1303	J Histochem Cytochem	HCAPLUS
Molberg, O	1998	4	713	Nat Med	HCAPLUS
Moscarello, M	1994	94	146	J Clin Invest	HCAPLUS
Muir, I	1980		27	The Joints and Synov	HCAPLUS
Nakashima, K	1999	274	27786	J Biol Chem	HCAPLUS
Nienhuis, R	1964	23	302	Ann Rheum Dis	MEDLINE
Paimela, L	1992	51	743	Ann Rheum Dis	MEDLINE
Palosuo, T	1998	115	294	Int Arch Allergy Imm	HCAPLUS
Paroczai, C	1988	21	117	Clin Biochem	MEDLINE
Piacentini, M	1999	20	130	Immunol Today	HCAPLUS
Ronday, H	1996	35	416	Br J Rheumatol	MEDLINE
Sagarriga, V	1996	328	135	Arch Biochem Biophys	
Schellekens, G	1998	101	273	J Clin Invest	HCAPLUS
Sebbag, M	1995	95	2672	J Clin Invest	HCAPLUS
Senshu, T	1992	203	94	Anal Biochem	HCAPLUS
Senshu, T	1995	105	163	J Invest Dermatol	HCAPLUS
Serre, G	1996		271	Autoantibodies	
Simon, M	1993	92	1387	J Clin Invest	HCAPLUS
Simon, M	1995	105	432	J Invest Dermatol	HCAPLUS
Tomasini-Johansson, B	1998	37	620	Br J Rheumatol	HCAPLUS
Utz, P	1998	41	1152	Arthritis Rheum	HCAPLUS
Utz, P	1997	185	843	J Exp Med	HCAPLUS
Vincent, C	1989	48	712	Ann Rheum Dis	MEDLINE
Vincent, C	1991	4	493	J Autoimmun	MEDLINE
Vincent, C	1998	25	838	J Rheumatol	HCAPLUS
Weinberg, J	1991	34	996	Arthritis Rheum	MEDLINE
Young, B	1979	2	97	Br Med J	HCAPLUS
Zacharski, L	1992	63	155	Clin Immunol Immunop	MEDLINE

L76 ANSWER 4 OF 7 HCAPLUS COPYRIGHT 2002 ACS
AN 2001:31538 HCAPLUS
DN 134:95494
TI **Citrulline**-containing fibrin derivatives, and their use for diagnosing or treating **rheumatoid arthritis**
IN **Serre, Guy; Sebbag, Mireille**
PA Universite Paul Sabatier - Toulouse III, Fr.

SO PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DT Patent
LA French
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001002437	A1	20010111	WO 2000-FR1857	20000630
W: CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
FR 2795735	A1	20010105	FR 1999-8470	19990701
FR 2795735	B1	20010907		
PRAI FR 1999-8470	A	19990701		

AB The invention provides **citrulline**-contg. polypeptides which are derived from fibrin and are useful for diagnosing or treating **rheumatoid arthritis**.
IT **372-75-8, Citrulline**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(**citrulline**-contg. fibrin derivs., and use for diagnosing or treating **rheumatoid arthritis**)
RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Raats, J	1998			WO 9822503 A	HCAPLUS
Scripps Research Inst	1995			WO 9528946 A	HCAPLUS

L76 ANSWER 5 OF 7 HCAPLUS COPYRIGHT 2002 ACS
AN 2000:867584 HCAPLUS
DN 134:278692
TI High levels of cytokeratin 19 fragments but no evidence of cytokeratins 1, 2, 10/11, 14 or **filaggrin** in the serum of squamous cell lung carcinoma patients
AU Miedouge, Marcel; Devys, Anne; **Simon, Michel**; Rouzaud, Philippe; Salama, Gilles; Reyre, Joelle; Pujazon, Marie-Christine; Carles, Pierre; **Serre, Guy**
CS Department of Biology and Pathology of the Cell, INSERM CJF 96-02 (IFR30, INSERM-CNRS-UPS-CHU), Toulouse Purpan School of Medicine, Purpan Hospital, University of Toulouse III, Toulouse, Fr.
SO Tumor Biology (2000), Volume Date 2001, 22(1), 19-26
CODEN: TUMBEA; ISSN: 1010-4283
PB S. Karger AG
DT Journal
LA English
AB The CYFRA 21-1 assay detects circulating fragments of cytokeratin 19, which is a sensitive marker for the diagnosis of lung cancers, particularly squamous cell carcinomas and adenocarcinomas. Epidermis-type proteins, such as cytokeratins 1, 2, 10/11 and 14 or **filaggrin**, are also expressed in squamous cell carcinomas. These could also be pertinent tumor markers, ideally as sensitive as CYFRA 21-1 and more specific for squamous cell lung cancer. To verify this hypothesis, using monoclonal **antibodies** produced in our lab., we developed immunoassays specific for these proteins. After optimization, the immunoassays were evaluated in sera from 91 controls and 138 patients with squamous cell lung cancer and compared to conventional tumor markers (CEA, SCC Ag and CYFRA 21-1). Less than 14% of the sera were above the lower limit of detection of the cytokeratin- and **filaggrin**-specific immunoassays. Moreover, part of these pos. sera were induced by the presence of interfering heterophilic **antibodies** in sera. Thus, in patients with squamous cell lung cancer, we confirmed the high diagnostic sensitivity of CYFRA 21-1 (55.6%) but were unable to detect significant levels of epidermis-type cytokeratins or **filaggrin**.
RETABLE

Referenced Author	Year	VOL	PG	Referenced Work	Referenced

(RAU)	(RPY)	(RVL)	(RPG)	(RWK)	File
American Thoracic Socie	1997	156	320	Am J Respir Crit Car	
Barbaud, A	1998	8	320	Eur J Dermatol	HCAPLUS
Blobel, G	1984	45	407	Virchows Arch B Cell	HCAPLUS
Bodenmuller, H	1992		137	Munich, Zuckschwerdt	
Broers, J	1988	48	3221	Cancer Res	HCAPLUS
Bruderman, I	1990	66	1817	Cancer	MEDLINE
Chen, Z	1996	156	1357	J Urol	HCAPLUS
Dale, B	1993		79	Molecular Biology of	HCAPLUS
Ebert, W	1994	32	189	Eur J Clin Chem Clin	HCAPLUS
Galvin, S	1989	4	277	Adv Dermatol	MEDLINE
Gazdar, A	1981		145	Small Cell Lung Canc	
Grosso, M	1990	34	51	Basic Appl Histochem	MEDLINE
Klein-Szanto, A	1984	108	888	Arch Pathol Lab Med	MEDLINE
Lara, C	1994	255	73	Arch Gynecol Obstet	MEDLINE
Leers, M	1997	27	179	Cytometry	HCAPLUS
Lynley, A	1983	744	28	Biochim Biophys Acta	HCAPLUS
Manabe, M	1991	48	43	Differentiation	MEDLINE
Molina, R	1994	15	318	Tumor Biol	MEDLINE
Moll, R	1991	41	117	Acta Histochem	
Moll, R	1992	140	427	Am J Pathol	MEDLINE
Moll, R	1982	31	11	Cell	HCAPLUS
Nakane, P	1974	22	1084	J Histochem Cytochem	HCAPLUS
Niklinski, J	1995	4	129	Eur J Cancer Prev	MEDLINE
Plebani, M	1995	72	170	Br J Cancer	MEDLINE
Pujol, J	1993	53	61	Cancer Res	HCAPLUS
Satoh, H	1997	16	597	Am J Respir Cell Mol	HCAPLUS
Scully, C	1993	22	246	J Oral Pathol Med	MEDLINE
Serre, G	1987	88	21	J Invest Dermatol	HCAPLUS
Serre, G	1991	97	1061	J Invest Dermatol	HCAPLUS
Serre, G	1988		524	Structure and Functi	
Simon, M	1993	92	1387	J Clin Invest	HCAPLUS
Simon, M	1995	105	432	J Invest Dermatol	HCAPLUS
Stieber, P	1993	31	689	Eur J Clin Chem Clin	HCAPLUS
Suminami, Y	1998	19	488	Tumor Biol	HCAPLUS
Sun, T	1978	253	2053	J Biol Chem	HCAPLUS
Thompson, R	1986	32	476	Clin Chem	HCAPLUS
Van Dorst, E	1998	51	679	J Clin Pathol	MEDLINE
Van der Gaast, A	1994	69	525	Br J Cancer	MEDLINE
Vigneswaran, N	1989	18	377	J Oral Pathol Med	MEDLINE
Wetzels, R	1992	20	295	Histopathology	MEDLINE

L76 ANSWER 6 OF 7 HCAPLUS COPYRIGHT 2002 ACS
AN 2000:231558 HCAPLUS
DN 133:236721
TI In the **rheumatoid** pannus, anti-**filaggrin** **autoantibodies** are produced by local plasma cells and constitute a higher proportion of IgG than in synovial fluid and serum
AU Masson-Bessiere, C.; **Sebbag, M.**; Durieux, J.-J.; Nogueira, L.; **Vincent, C.**; **Girbal-Neuhauser, E.**; Durroux, R.; Cantagrel, A.; **Serre, G.**
CS Department of Biology and Pathology of the Cell, Institut National de la Sante et de la Recherche Medicale, Toulouse, 31059, Fr.
SO Clin. Exp. Immunol. (2000), 119(3), 544-552
CODEN: CEXIAL; ISSN: 0009-9104
PB Blackwell Science Ltd.
DT Journal
LA English
AB IgG anti-**filaggrin** **autoantibodies** (AFA) are the most specific serol. markers of **rheumatoid** **arthritis** (RA). They include the so-called 'anti-keratin **antibodies**' (AKA) and anti-perinuclear factor (APF), and recognize human epidermal **filaggrin** and other (pro)**filaggrin**-related proteins of various epithelial tissues. In this study we demonstrate that AFA are produced in **rheumatoid** synovial joints. In 31 RA patients, AFA

levels were assayed at equal IgG concns. in paired synovial fluids (SF) and sera. AFA titer-like values detd. by indirect immunofluorescence and immunoblotting and AFA concns. detd. by ELISA were non-significantly different in serum and SF, clearly indicating that AFA are not concd. in SF. In contrast, we demonstrated that AFA are enriched in RA synovial membranes, since the ELISA-detd. AFA in low ionic-strength exts. of synovial tissue from four RA patients represented a 7.5-fold higher proportion of total IgG than in paired sera. When small synovial tissue explants from RA patients were cultured for a period of 5 wk, the profile of IgG and AFA released in the culture supernatants was first consistent with passive diffusion of the tissue-infiltrating IgG (including AFA) over the first day of culture, then with a de novo synthesis of IgG and AFA. Therefore, AFA-secreting plasma cells are present in the synovial tissue of RA patients and AFA can represent a significant proportion of the IgG secreted within the **rheumatoid** pannus.

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Arnett, F	1988	31	315	Arthritis Rheum	MEDLINE
Bang, H	1994	81	322	Immunology	HCAPLUS
Blass, S	1995	54	355	Ann Rheum Dis	MEDLINE
Brown, K	1995	41	509	Scand J Immunol	MEDLINE
Clague, R	1984	27	1370	Arthritis Rheum	MEDLINE
Cush, J	1991	265	9	Clin Orthop	
Despres, N	1995	95	1891	J Clin Invest	HCAPLUS
Despres, N	1994	21	1027	J Rheumatol	HCAPLUS
Egeland, T	1982	16	413	Scand J Immunol	MEDLINE
Gause, A	1995	25	2775	Eur J Immunol	HCAPLUS
Girbal, E	1993	52	749	Ann Rheum Dis	HCAPLUS
Girbal-Neuhauser, E	1999	162	585	J Immunol	HCAPLUS
Harris, E	1990	332	1277	N Engl J Med	
Kirstein, H	1989	97	185	Acta Pathol Microbio	MEDLINE
Klareskog, L	1990	118	285	Immunol Rev	HCAPLUS
Konttinen, Y	1981	24	71	Arthritis Rheum	MEDLINE
Koopman, W	1985	28	1219	Arthritis Rheum	MEDLINE
Kurki, P	1992	35	914	Arthitis Rheum	MEDLINE
Levick, J	1981	24	1550	Arthritis Rheum	HCAPLUS
Loewi, G	1974	1	34	J Rheumatol	MEDLINE
Matsubara, T	1987	30	18	Arthritis Rheum	MEDLINE
Meyer, O	1997	56	682	Ann Rheum Dis	MEDLINE
Mimori, T	1995	92	7267	Proc Natl Acad Sci U	HCAPLUS
Moynier, M	1992	35	49	Arthritis Rheum	MEDLINE
Munthe, E	1972	12	55	Clin Exp Immunol	MEDLINE
Munthe, E	1972	1	217	Scand J Immunol	HCAPLUS
Natvig, J	1989	11	301	Springer Semin Immun	HCAPLUS
Nienhuis, R	1964	23	302	Ann Rheum Dis	MEDLINE
Osung, O	1982	41	69	Ann Rheum Dis	MEDLINE
Otten, H	1993	94	236	Clin Exp Immunol	HCAPLUS
Paimela, L	1992	51	743	Ann Rheum Dis	MEDLINE
Quismorio, F	1983	26	494	Arthritis Rheum	
Randen, I	1992	148	3296	J Immunol	HCAPLUS
Randen, I	1995	41	481	Scand J Immunol	MEDLINE
Ronnelid, J	1994	37	1023	Arthritis Rheum	MEDLINE
Rudolphi, U	1997	40	1409	Arthritis Rheum	HCAPLUS
Schellekens, G	1998	101	273	J Clin Invest	HCAPLUS
Schroder, A	1996	93	221	Proc Natl Acad Sci U	MEDLINE
Sebbag, M	1995	95	2672	J Clin Invest	HCAPLUS
Serre, G	1986	53	607	Rev Rhum Mal Osteoar	MEDLINE
Simon, M	1993	92	1387	J Clin Invest	HCAPLUS
Simon, S	1995	105	462	J Invest Dermatol	
Sliwinski, A	1970	76	304	J Lab Clin Med	MEDLINE
Smiley, J	1968	47	624	J Clin Invest	HCAPLUS
Steiner, G	1992	90	1061	J Clin Invest	HCAPLUS
Terato, K	1990	33	1493	Arthritis Rheum	MEDLINE
Tuaillon, N	1990	91	297	Int Arch Allergy App	MEDLINE

Van Boxel, J	1975	293	517	N Engl J Med	MEDLINE
Vaughan, J	1993	36	1	Arthritis Rheum	HCAPLUS
Vincent, C	1989	48	712	Ann Rheum Dis	MEDLINE
Vincent, C	1998	25	838	J Rheumatol	HCAPLUS
Vivino, F	1990	33	960	Arthritis Rheum	MEDLINE
Wernick, R	1985	28	742	Arthritis Rheum	MEDLINE
Youinou, P	1985	44	450	Ann Rheum Dis	MEDLINE
Youinou, P	1995	107	508	Int Arch Allergy Imm	HCAPLUS
Young, B	1979	2	97	Br Med J	HCAPLUS

L76 ANSWER 7 OF 7 HCAPLUS COPYRIGHT 2002 ACS
AN 1999:33223 HCAPLUS
DN 130:195491
TI The epitopes targeted by the **rheumatoid arthritis** -associated **antifilaggrin autoantibodies** are posttranslationally generated on various sites of (pro)**filaggrin** by deimination of **arginine** residues
AU **Girbal-Neuhauser, Elisabeth**; Durieux, Jean-Jacques; **Arnaud, Michel**; **Dalbon, Pascal**; **Sebbag, Mireille**; **Vincent, Christian**; **Simon, Michel**; Senshu, Tatsuo; Masson-Bessiere, Christine; **Jolivet-Reynaud, Colette**; **Jolivet, Michel**; **Serre, Guy**
CS Department of Biology and Pathology of the Cell, Institut National de la Sante et de la Recherche MedicaleT, Toulouse-Purpan School of Medicine, University Toulouse III, Toulouse, Fr.
SO J. Immunol. (1999), 162(1), 585-594
CODEN: JOIMA3; ISSN: 0022-1767
PB American Association of Immunologists
DT Journal
LA English
AB **Antifilaggrin autoantibodies** (AFA) are a population of IgG **autoantibodies** assocd. to **rheumatoid arthritis** (RA), which includes the so-called "antikeratin" Abs and antiperinuclear factor. AFA are the most specific serol. markers of RA. We previously showed that they recognize human epidermal **filaggrin** and other **profilaggrin**-related proteins of various epithelial tissues. Here, we report further characterization of the protein Ags and epitopes targeted by AFA. All the Ags that exhibit numerous neutral/acidic isoelec. variants were immunochem. demonstrated to be deiminated proteins. In vitro deimination of a recombinant human **filaggrin** by a peptidylarginine deiminase generated AFA epitopes on the protein. Moreover, two of three **filaggrin**-derived synthetic peptides with a **citrulline** in the central position were specifically and widely recognized by AFA affinity-purified from a series of RA sera. These results indicate that **citrulline** residues are constitutive of the AFA epitopes, but only in the context of specific amino acid sequences of **filaggrin**. In competition expts., the two peptides abolished the AFA reactivity of RA sera, showing that they present major AFA epitopes. These data should help in the identification of a putative deiminated AFA-inducing or cross-reactive articular autoantigen and provide new insights into the pathogenesis of RA. They could also open the way toward specific immunosuppressive and/or preventive therapy of RA.
IT **74-79-3**, L-**Arginine**, biological studies **372-75-8**, L-**Citrulline**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(epitopes targeted by **rheumatoid arthritis**-assocd. **antifilaggrin autoantibodies** are posttranslationally generated on various sites of (pro)**filaggrin** by deimination of **arginine** residues)

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Arnett, F	1988	31	315	Arthritis Rheum	MEDLINE
Bang, H	1994	81	322	Immunology	HCAPLUS

Blass, S	1995	54	355	Ann Rheum Dis	MEDLINE
Boers, M	1997	350	309	Lancet	HCAPLUS
Chan, K	1993	37	814	Arthritis Rheum	
Dale, B	1990		393	Cellular and Molecul	
Deibel, M	1989	2	189	Peptide Res	HCAPLUS
Despres, N	1995	95	1891	J Clin Invest	HCAPLUS
Despres, N	1994	21	1027	J Rheumatol	HCAPLUS
Durieux, J	1997	64	601	Rev Rhum	
Finch, P	1971	15	145	FEBS Lett	HCAPLUS
Gan, S	1990	29	9432	Biochemistry	HCAPLUS
Girbal, E	1993	52	749	Ann Rheum Dis	HCAPLUS
Girbal-Neuhauser, E	1997	3	145	Mol Med	HCAPLUS
Girbal-Neuhauser, E	1997	64	74	Rev Rhum	
Gomes-Daudrix, V	1994	53	735	Ann Rheum Dis	MEDLINE
Harding, C	1983	170	651	J Mol Biol	HCAPLUS
Hoet, R	1992		299	Rheumatoid Arthritis	
Johnson, G	1981	40	263	Ann Rheum Dis	MEDLINE
Kirstein, H	1987	16	331	Scand J Rheumatol	MEDLINE
Kubilus, J	1980	615	246	Biochim Biophys Acta	HCAPLUS
Kurki, P	1992	35	914	Arthritis Rheum	MEDLINE
Lamensa, J	1993	61	987	J Neurochem	HCAPLUS
Li, S	1996		520	Autoantibodies	
Lonsdale-Eccles, J	1982	21	5940	Biochemistry	HCAPLUS
Mastronardi, F	1996	97	349	J Clin Invest	HCAPLUS
McKinley-Grant, L	1989	86	4848	Proc Natl Acad Sci U	HCAPLUS
Mimori, T	1995	92	7267	Proc Natl Acad Sci U	HCAPLUS
Moscarello, M	1994	94	146	J Clin Invest	HCAPLUS
Nagata, S	1990	64	72	Experientia	
Nienhuis, R	1964	23	302	Ann Rheum Dis	MEDLINE
Paimela, L	1992	51	743	Ann Rheum Dis	MEDLINE
Quismorio, F	1983	26	494	Arthritis Rheum	
Schellekens, G	1998	101	273	J Clin Invest	HCAPLUS
Scott, I	1981	669	65	Biochim Biophys Acta	HCAPLUS
Sebbag, M	1995	95	2672	J Clin Invest	HCAPLUS
Senshu, T	1992	203	94	Anal Biochem	HCAPLUS
Senshu, T	1996	225	712	Biochim Biophys Res	HCAPLUS
Senshu, T	1995	105	163	J Invest Dermatol	HCAPLUS
Serre, G	1986	53	607	Rev Rhum Mal Osteoar	MEDLINE
Simon, M	1995	100	90	Clin Exp Immunol	MEDLINE
Simon, M	1993	92	1387	J Clin Invest	HCAPLUS
Simon, M	1995	105	432	J Invest Dermatol	HCAPLUS
Steiner, G	1992	90	1061	J Clin Invest	HCAPLUS
Sugawara, K	1982	91	1065	J Biochem	HCAPLUS
Tarsca, E	1996	271	30709	J Biol Chem	
Terakawa, H	1991	110	661	J Biochem	HCAPLUS
Terato, K	1990	33	1493	Arthritis Rheum	MEDLINE
Utz, P	1997	185	843	J Exp Med	HCAPLUS
Vincent, C	1989	48	712	Ann Rheum Dis	MEDLINE
Vincent, C	1998	25	838	J Rheumatol	HCAPLUS
Visser, H	1997	40	S289	Arthritis Rheum	
Watanabe, K	1988	966	375	Biochim Biophys Acta	HCAPLUS
Wood, D	1989	264	5121	J Biol Chem	HCAPLUS
Wucherpfennig, K	1997	100	1114	J Clin Invest	HCAPLUS
Young, B	1979	2	97	Br Med J	HCAPLUS

=> fil reg
FILE 'REGISTRY' ENTERED AT 09:23:33 ON 14 MAR 2002

STRUCTURE FILE UPDATES: 12 MAR 2002 HIGHEST RN 400707-37-1
DICTIONARY FILE UPDATES: 12 MAR 2002 HIGHEST RN 400707-37-1

TSCA INFORMATION NOW CURRENT THROUGH July 7, 2001

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Calculated physical property data is now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

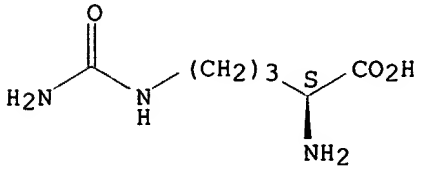
The P indicator for Preparations was not generated for all of the CAS Registry Numbers that were added to the H/Z/CA/CAplus files between 12/27/01 and 1/23/02. Use of the P indicator in online and SDI searches during this period, either directly appended to a CAS Registry Number or by qualifying an L-number with /P, may have yielded incomplete results. As of 1/23/02, the situation has been resolved. Also, note that searches conducted using the PREP role indicator were not affected.

Customers running searches and/or SDIs in the H/Z/CA/CAplus files incorporating CAS Registry Numbers with the P indicator between 12/27/01 and 1/23/02, are encouraged to re-run these strategies. Contact the CAS Help Desk at 1-800-848-6533 in North America or 1-614-447-3698, worldwide, or send an e-mail to help@cas.org for further assistance or to receive a credit for any duplicate searches.

=> d ide can tot l79

L79 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2002 ACS
RN **372-75-8** REGISTRY
CN L-Ornithine, N5-(aminocarbonyl)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Ornithine, N5-carbamoyl-, L- (8CI)
OTHER NAMES:
CN .alpha.-Amino-.delta.-ureidovaleric acid
CN .delta.-Ureidonorvaline
CN **Citrulline**
CN L-Citrulline
CN N.delta.-Carbamylornithine
CN N5-Carbamoyl-L-ornithine
FS STEREOSEARCH
MF C6 H13 N3 O3
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, EMBASE, HODOC*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PIRA, PROMT, SPECINFO, TOXCENTER, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2761 REFERENCES IN FILE CA (1967 TO DATE)
47 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
2770 REFERENCES IN FILE CAPLUS (1967 TO DATE)
69 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 136:166339

REFERENCE 2: 136:166267

REFERENCE 3: 136:164142

REFERENCE 4: 136:161358

REFERENCE 5: 136:150437

REFERENCE 6: 136:149068

REFERENCE 7: 136:147260

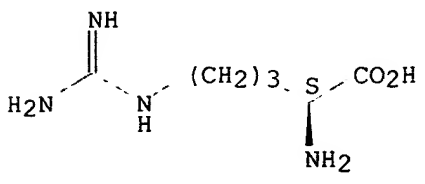
REFERENCE 8: 136:139824

REFERENCE 9: 136:130724

REFERENCE 10: 136:117568

L79 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2002 ACS
RN **74-79-3** REGISTRY
CN L-Arginine (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Arginine, L- (8CI)
OTHER NAMES:
CN (S)-2-Amino-5-[(aminoiminomethyl)amino]pentanoic acid
CN **Arginine**
CN L-(+)-Arginine
CN L-.alpha.-Amino-.delta.-guanidinovaleric acid
CN L-Arg
CN L-Norvaline, 5-[(aminoiminomethyl)amino]-
CN L-Ornithine, N5-(aminoiminomethyl)-
CN Pentanoic acid, 2-amino-5-[(aminoiminomethyl)amino]-, (S)-
FS STEREOSEARCH
DR 7004-12-8, 142-49-4
MF C6 H14 N4 O2
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DDFU, DETHERM*, DIOGENES, DRUGU, EMBASE, GMELIN*, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PHAR, PIRA, PROMT, RTECS*, SPECINFO, TOXCENTER, TULSA, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

29669 REFERENCES IN FILE CA (1967 TO DATE)
887 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
29737 REFERENCES IN FILE CAPLUS (1967 TO DATE)
6 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 136:177215

REFERENCE 2: 136:172778

REFERENCE 3: 136:172468

REFERENCE 4: 136:167651

REFERENCE 5: 136:167388

REFERENCE 6: 136:166719

REFERENCE 7: 136:166655

REFERENCE 8: 136:166653

REFERENCE 9: 136:166445

REFERENCE 10: 136:166348

=> fil biosis
FILE 'BIOSIS' ENTERED AT 10:05:02 ON 14 MAR 2002
COPYRIGHT (C) 2002 BIOLOGICAL ABSTRACTS INC.(R)

FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 13 March 2002 (20020313/ED)

=> d all tot l100

L100 ANSWER 1 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:497088 BIOSIS
DN PREV199800497088
TI Deimination of 70-kD nuclear protein during epidermal apoptotic events in vitro.
AU Mizoguchi, Masayuki; Manabe, Motomu (1); Kawamura, Yasushi; Kondo, Yukiko; Ishidoh, Kazumi; Kominami, Eiki; Watanabe, Kazutaka; Asaga, Hiroaki; Senshu, Tatsuo; Ogawa, Hideoki
CS (1) Dep. Dermatol., Untendo Univ. Sch. Med., Hongo 3-1-3, Bunkyo-ku, Tokyo 113 Japan
SO Journal of Histochemistry and Cytochemistry, (**Nov., 1998**) Vol. 46, No. 11, pp. 1303-1309.
ISSN: 0022-1554.
DT Article
LA English
AB Peptidylarginine deiminase (PAD) is the enzyme responsible for converting protein-bound **arginine** residues to **citrulline**. It has recently been shown that a number of epidermal proteins, including **filaggrin**, trichohyalin, and keratins, are deiminated by the action of PAD, suggesting a possible role for protein deimination during the final stages of epidermal differentiation. We report here a novel PAD substrate found during the course of identifying deiminated proteins in cultured rat epidermal keratinocytes. We found that a 70-kD protein localized to the periphery of the nucleus was preferentially deiminated

after ionomycin treatment in the presence of 2 mM calcium and was associated with apoptotic events in these cells. Furthermore, we discovered that the deimination of nuclear protein could be induced by transfection of a PAD cDNA into rat epidermal keratinocytes. These data suggest that PAD may act on the 70-kD nuclear protein to induce disassembly of the nuclear lamina and promote apoptosis during terminal epidermal differentiation.

CC Integumentary System - General; Methods *18501
Biochemical Methods - General *10050
Biochemical Studies - General *10060

BC Muridae 86375

IT Major Concepts
Biochemistry and Molecular Biophysics; Integumentary System (Chemical Coordination and Homeostasis); Methods and Techniques

IT Parts, Structures, & Systems of Organisms
epidermal keratinocyte: integumentary system

IT Chemicals & Biochemicals
nuclear protein: analysis, deimination

IT Methods & Equipment
protein analysis: analysis/characterization techniques: CB, analytical method

IT Miscellaneous Descriptors
apoptosis

ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
rat (Muridae)

ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates

L100 ANSWER 2 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

AN 1998:470056 BIOSIS

DN PREV199800470056

TI Increased frequency of **antifilaggrin antibody** in patients with **rheumatoid arthritis**.

AU Song, Yeong Wook (1); Lee, Eun Bong (1); Baek, Han Ioo (1); Chung, Eun Sook (1); Kim, Hyun Ah (1); Kim, In Guy; Choi, Kyung Ho

CS (1) Dep. Intern. Med., Seoul Natl. Univ. Coll. Med., Seoul 110-744 South Korea

SO Arthritis & Rheumatism, (**Sept., 1998**) Vol. 41, No. 9 SUPPL., pp. S312.
Meeting Info.: 62nd National Scientific Meeting of the American College of Rheumatology and the 33rd National Scientific Meeting of the Association of Rheumatology Health Professionals San Diego, California, USA November 8-12, 1998 American College of Rheumatology
. ISSN: 0004-3591.

DT Conference

LA English

CC **Bones, Joints, Fasciae, Connective and Adipose Tissue - General; Methods *18001**
Immunology and Immunochemistry - General; Methods *34502
General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520

BC Hominidae 86215

IT Major Concepts
Rheumatology (Human Medicine, Medical Sciences)

IT Diseases
rheumatoid arthritis: connective tissue disease, immune system disease, joint disease

IT Chemicals & Biochemicals
antifilaggrin antibody: frequency

IT Miscellaneous Descriptors
Meeting Abstract; Meeting Poster

ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
human (Hominidae): patient
ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates

L100 ANSWER 3 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:468693 BIOSIS
DN PREV199800468693
TI Epitope mapping of natural **filaggrin** leads to the identification of **rheumatoid arthritis**-immunoreactive epitopes containing **citrulline**.
AU Union, Ann (1); Amerijckx, Liesbet (1); Raymackers, Jos (1); Dauwe, Martine (1); De Keyser, Filip; Veys, Eric; Meheus, Lydie (1)
CS (1) Innogenetics N.V., Industriepark 7, 9052 Ghent Belgium
SO Arthritis & Rheumatism, (**Sept., 1998**) Vol. 41, No. 9 SUPPL., pp. S84.
Meeting Info.: 62nd National Scientific Meeting of the American College of Rheumatology and the 33rd National Scientific Meeting of the Association of Rheumatology Health Professionals San Diego, California, USA November 8-12, 1998 American College of Rheumatology
. ISSN: 0004-3591.
DT Conference
LA English
CC Biochemical Studies - General *10060
Immunology and Immunochemistry - General; Methods *34502
General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
IT Major Concepts
Biochemistry and Molecular Biophysics
IT Diseases
rheumatoid arthritis: connective tissue disease, immune system disease, joint disease
IT Chemicals & Biochemicals
citrulline; filaggrin; rheumatoid arthritis-immunoreactive epitopes
IT Methods & Equipment
epitope mapping: analytical method
IT Miscellaneous Descriptors
Meeting Abstract; Meeting Poster
RN **372-75-8 (CITRULLINE)**

L100 ANSWER 4 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:382001 BIOSIS
DN PREV199800382001
TI **Rheumatoid** factor detected by ELISA, anti-**filaggrin antibodies** are useful markers for early diagnosis of community cases of **rheumatoid arthritis**.
AU Vittecoq, O. (1); Jouen-Beades, F.; Krzanowska, K.; Delpech, A.; Menard, J. F.; Daragon, A.; Bichon-Tauvel, I.; Tron, F.; Le Loet, X.
CS (1) Dep. Rheumatol., Groupe de Recherche en ImmunoPathol., IFR 23, CHU de Rouen, 76031 Rouen cedex France
SO British Journal of Rheumatology, (1998) Vol. 37, No. ABSTR. SUPPL. 1, pp. 83.
Meeting Info.: XVth Annual General Meeting of the British Society for Rheumatology held jointly with the Spanish Society for Rheumatology and the British Health Professionals in Rheumatology Spring Meeting Brighton, England, UK April 22-24, 1998 British Society for Rheumatology
. ISSN: 0263-7103.
DT Conference
LA English
CC **Immunology and Immunochemistry - General; Methods *34502**
Biochemical Methods - General *10050
Biochemical Studies - General *10060
Pathology, General and Miscellaneous - Diagnostic *12504
Bones, Joints, Fasciae, Connective and Adipose Tissue - Pathology *18006

Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508
General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
BC Hominidae 86215
IT Major Concepts
Clinical Immunology (Human Medicine, Medical Sciences); Methods and Techniques; **Rheumatology** (Human Medicine, Medical Sciences)
IT Diseases
rheumatoid arthritis: connective tissue disease, joint disease, immune system disease, diagnosis
IT Chemicals & Biochemicals
anti-**filaggrin antibody**; **rheumatoid** factor: detection
IT Methods & Equipment
rheumatoid factor ELISA: diagnostic method
IT Miscellaneous Descriptors
Meeting Abstract
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae): patient
ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates

L100 ANSWER 5 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:272217 BIOSIS
DN PREV199800272217
TI Diagnostic value of **antibodies** to **filaggrin** in **rheumatoid arthritis**.
AU Slack, Shawn L. (1); Mannik, Mart; Dale, Beverly A.
CS (1) Div. Rheumatol., Univ. Washington, Box 356428, Seattle, WA 98195-6428 USA
SO Journal of Rheumatology, (**May, 1998**) Vol. 25, No. 5, pp. 847-851.
ISSN: 0315-162X.
DT Article
LA English
AB Objective. To determine the prevalence of **antibodies** to **filaggrin** in a cross sectional sample of patients with **rheumatoid arthritis** (RA). Methods. **Filaggrin** from human skin was either extracted with 0.05% Nonidet P-40 and then partially purified by precipitating in ethanol and resuspending in water (Nonidet preparation) or extracted with 9 M urea and then purified by sequential fractionation on a DEAE Sephadex column and on a strong cation exchange column (purified preparation). **Antibodies** to **filaggrin** were detected using immunoblotting techniques with sera diluted 1:50. Antikeratin **antibodies** (AKA) were detected using indirect immunofluorescence microscopy on sections of rat esophagus. Results. **Antibodies** to **filaggrin** were detected in 5 of 30 sera of patients with RA using **filaggrin** from the Nonidet preparation and 6 of 49 sera using **filaggrin** from the purified preparation. AKA were detected in 13 of 40 sera. A positive correlation existed between the presence of AKA and the presence of **antibodies** to **filaggrin** using the purified preparation ($p = 0.017$). Conclusion. These data indicate that the reactivity of RA sera with **filaggrin** is not identical to the presence of AKA and is variable depending upon the preparation of **filaggrin** used. The diagnostic value of **antibodies** to **filaggrin** remains to be proven.
CC **Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508**
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biochemical Studies - Carbohydrates *10068
Pathology, General and Miscellaneous - Diagnostic *12504
Pathology, General and Miscellaneous - Inflammation and Inflammatory

Disease *12508
Bones, Joints, Fasciae, Connective and Adipose Tissue - Pathology *18006
Immunology and Immunochemistry - General; Methods *34502
BC Hominidae 86215
IT Major Concepts
Clinical Immunology (Human Medicine, Medical Sciences);
Rheumatology (Human Medicine, Medical Sciences)
IT Diseases
rheumatoid arthritis: connective tissue disease, immune system disease, joint disease
IT Chemicals & Biochemicals
anti-**filaggrin antibodies**: diagnostic value; antikeratin **antibodies**; autoantigen; **filaggrin**
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae): patient
ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates

L100 ANSWER 6 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:272216 BIOSIS
DN PREV199800272216
TI Immunoblotting detection of **autoantibodies** to human epidermis **filaggrin**: A new diagnostic test for **rheumatoid arthritis**.
AU Vincent, Christian (1); Simon, Michel; Sebbag, Mireille; Girbal-Neuhauser, Elisabeth; Durieux, Jean-Jacques; Cantagrel, Alain; Fournié, Bernard; Mazieres, Bernard; Serre, Guy
CS (1) Lab. Biol. Cell. Cytol., Hop. Purpan, Place du Dr. Baylac, 31059 Toulouse Cedex France
SO Journal of Rheumatology, (**May, 1998**) Vol. 25, No. 5, pp. 838-846.
ISSN: 0315-162X.
DT Article
LA English
AB Objective. We previously reported that so-called antikeratin **antibodies** (AKA) and antiperinuclear factor (APF) recognize epitope(s) present on human epidermal **filaggrin**. In the present study, we developed a new diagnostic test for **rheumatoid arthritis** (RA) based on detection of **antifilaggrin autoantibodies** (AFA) by immunoblotting. Methods. We tested 670 serum samples, including 190 RA. AFA titers were estimated by immunoblotting on **filaggrin** enriched human epidermis extracts, and AKA titers by indirect immunofluorescence (IIF) on rat esophagus epithelium. Diagnostic values of the tests were compared. Results. Each test resulted in diagnosis of more than 40% of RA samples, with a specificity of 0.99. Although the tests were strongly correlated, their association allowed the diagnosis of more than 60% of RA samples, with the same specificity. Conclusion. Immunoblot detection of AFA, a simple and standardizable test, may be an alternative or complement to conventional IIF detection of AKA.
CC **Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508**
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biochemical Studies - Carbohydrates *10068
Pathology, General and Miscellaneous - Diagnostic *12504
Pathology, General and Miscellaneous - Inflammation and Inflammatory Disease *12508
Bones, Joints, Fasciae, Connective and Adipose Tissue - Pathology *18006
Immunology and Immunochemistry - General; Methods *34502
Biophysics - General Biophysical Techniques *10504
BC Hominidae 86215
IT Major Concepts

Clinical Immunology (Human Medicine, Medical Sciences); Methods and Techniques; **Rheumatology** (Human Medicine, Medical Sciences)
IT Diseases
rheumatoid arthritis: connective tissue disease, immune system disease, joint disease
IT Chemicals & Biochemicals
antifilaggrin autoantibodies: immunoblot detection; antikeratin **antibodies**; human epidermis **filaggrin autoantibodies**
IT Methods & Equipment
immunoblotting: diagnostic method
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae): patient
ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates

L100 ANSWER 7 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:257385 BIOSIS
DN PREV199800257385
TI Purification of **filaggrin** from human epidermis and measurement of **antifilaggrin autoantibodies** in sera from patients with **rheumatoid arthritis** by an enzyme-linked immunosorbent assay.
AU Palosuo, T. (1); Lukka, M.; Alenius, H.; Kalkkinen, N.; Aho, K.; Kurki, P.; Heikkila, R.; Nykanen, M.; Von Essen, R.
CS (1) Lab. Immunobiol., Natl. Public Health Inst., Mannerheimintie 166, FIN-00300 Helsinki Finland
SO International Archives of Allergy and Immunology, (**April, 1998**) Vol. 115, No. 4, pp. 294-302.
ISSN: 1018-2438.
DT Article
LA English
AB Background: The so-called antikeratin **antibody** (AKA) and the antiperinuclear factor (APF) that recognize proteins related to human epidermal **filaggrin** belong to the most specific serological markers of **rheumatoid arthritis** (RA). However, assays for the detection of AKA and APF are currently based on immunofluorescence, a method that is subject to arbitrary interpretation and inadequate standardization of the substrates. Methods: Proteins extracted from human epidermis were separated by reversed-phase high-performance liquid chromatography (HPLC). **Filaggrin** -containing fractions, identified in immunoblotting by monoclonal **antifilaggrin antibodies**, were then subjected to gel filtration HPLC and, finally, to a second reversed-phase HPLC step. Tryptic digestion, amino acid sequencing and mass spectrometry were used to confirm the identity of the purified protein. **Filaggrin** was used as antigen in enzyme-linked immunosorbent assay (ELISA) to measure IgG class **antifilaggrin antibodies**. Results: The **filaggrin** preparation obtained gave a single band in sodium dodecyl sulfate-polyacrylamide gel electrophoresis, binding monoclonal **antifilaggrin antibody** in immunoblotting. Amino acid sequences of all 10 tryptic peptides analyzed were shown to originate from human **filaggrin**. **Antifilaggrin antibody** levels exceeded the 99th percentile level of 100 middle-aged blood donors in 26/55 (47%) RA sera. At a similar cutoff level 28/55 (51%) of the RA sera were positive in the AKA test. Of the 26 **antifilaggrin** -positive sera, 21 were also AKA-positive. Conclusion: Human **filaggrin** can be purified by standard biochemical techniques, despite the heterogeneity of the protein, and used in ELISA for testing **autoantibodies** to **filaggrin**. The sensitivity of the assay equals that of the AKA test.
CC **Immunology and Immunochemistry - General; Methods** *34502
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biochemical Studies - Carbohydrates *10068

Biophysics - General Biophysical Techniques *10504
Biophysics - Molecular Properties and Macromolecules *10506
Pathology, General and Miscellaneous - Inflammation and Inflammatory Disease *12508
Bones, Joints, Fasciae, Connective and Adipose Tissue - Pathology *18006
Integumentary System - Physiology and Biochemistry *18504
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508
BC Hominidae 86215
IT Major Concepts
Biochemistry and Molecular Biophysics; Clinical Immunology (Human Medicine, Medical Sciences); Methods and Techniques
IT Parts, Structures, & Systems of Organisms
epidermis: integumentary system
IT Diseases
rheumatoid arthritis: connective tissue disease, immune system disease, joint disease
IT Chemicals & Biochemicals
antifilaggrin autoantibodies; antikeratin **antibody**: diagnostic marker; antiperinuclear factor: diagnostic marker; **filaggrin**
IT Methods & Equipment
amino acid sequencing: analytical method; mass spectrometry: analytical method; reversed-phase high-performance liquid chromatography: purification method; tryptic digestion: analytical method; ELISA: analytical method
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates

L100 ANSWER 8 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:158398 BIOSIS
DN PREV199800158398
TI The modified **arginine** residue **citrulline** is the major constituent of epitopes recognized by **autoantibodies** in sera from **rheumatoid arthritis** patients.
AU Schellekens, G. A. (1); De Jong, B. A. W. (1); Van Den Hoogen, F. H. J.; Van De Putte, L. B. A.; Van Venrooij, W. J. (1)
CS (1) Dep. Biochem., Univ. Nijmegen, Nijmegen Netherlands
SO Arthritis & Rheumatism, (**Sept., 1997**) Vol. 40, No. 9 SUPPL., pp. S276.
Meeting Info.: 61st National Scientific Meeting of the American College of Rheumatology and the 32nd National Scientific Meeting of the Association of Rheumatology Health Professionals Washington, DC, USA November 8-12, 1997 Association of Rheumatology Health Professionals
. ISSN: 0004-3591.
DT Conference
LA English
CC **Immunology and Immunochemistry - General; Methods *34502**
Biochemical Studies - General *10060
Bones, Joints, Fasciae, Connective and Adipose Tissue - General; Methods *18001
General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
BC Hominidae 86215
IT Major Concepts
Immune System (Chemical Coordination and Homeostasis)
IT Parts, Structures, & Systems of Organisms
serum: blood and lymphatics
IT Diseases
rheumatoid arthritis: connective tissue disease, immune system disease, joint disease

IT Chemicals & Biochemicals
antikeratin **antibodies**; antiperinuclear factor; **citrullinated** peptides; **citrulline**; **filaggrin** ; IgG **antibodies** [immunoglobulin G **antibodies**]
IT Miscellaneous Descriptors
epitope recognition; Meeting Abstract; Meeting Poster
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates
RN **74-79-3Q (ARGININE)**
7200-25-1Q (ARGININE)
372-75-8 (CITRULLINE)

L100 ANSWER 9 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:158262 BIOSIS
DN PREV199800158262
TI **Rheumatoid** factor detected by ELISA, anti-**filaggrin** and anti-Sa **antibodies** are useful markers for early diagnosis of community cases of **rheumatoid arthritis**.
AU Vittecoq, O. (1); Jouen-Beades, F.; Krzanowska, K.; Delpech, A.; Menard, J. F.; Daragon, A.; Tron, F.; Le Loet, X.
CS (1) Dep. Rheumatol., Groupe de Recherche en ImmunoPathol., IFR 23, CHU de Rouen, 76031 Rouen Cedex France
SO Arthritis & Rheumatism, (**Sept., 1997**) Vol. 40, No. 9 SUPPL., pp. S253.
Meeting Info.: 61st National Scientific Meeting of the American College of Rheumatology and the 32nd National Scientific Meeting of the Association of Rheumatology Health Professionals Washington, DC, USA November 8-12, 1997 Association of Rheumatology Health Professionals
. ISSN: 0004-3591.
DT Conference
LA English
CC **Bones, Joints, Fasciae, Connective and Adipose Tissue - General; Methods *18001**
Immunology and Immunochemistry - General; Methods *34502
General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
IT Major Concepts
Biochemistry and Molecular Biophysics
IT Diseases
rheumatoid arthritis: connective tissue disease, immune system disease, joint disease
IT Chemicals & Biochemicals
anti-**filaggrin**; anti-Sa **antibodies**; antikeratin; antiperinuclear factor; **rheumatoid** factor
IT Miscellaneous Descriptors
diagnosis; Meeting Abstract; Meeting Poster

L100 ANSWER 10 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:94121 BIOSIS
DN PREV199800094121
TI **Citrulline** is an essential constituent of antigenic determinants recognized by **rheumatoid arthritis**-specific **autoantibodies**.
AU Schellekens, Gerard A. (1); De Jong, Ben A. W.; Van Den Hoogen, Frank H. J.; Van De Putte, Leo B. A.; Van Venrooij, Walther J.
CS (1) Dep. Biochemistry, Univ. Nijmegen, PO Box 9101, 6500 HB Nijmegen Netherlands
SO Journal of Clinical Investigation, (**Jan., 1998**) Vol. 101, No. 1, pp. 273-281.
ISSN: 0021-9738.
DT Article
LA English

AB Only a few **autoantibodies** that are more or less specific for RA have been described so far. The **rheumatoid** factor most often tested for is not very specific for RA, while the more specific antiperinuclear factor for several reasons is not routinely used as a serological parameter. Here we show that **autoantibodies** reactive with synthetic peptides containing the unusual amino acid **citrulline**, a posttranslationally modified **arginine** residue, are specifically present in the sera of RA patients. Using several **citrulline**-containing peptide variants in ELISA, **antibodies** could be detected in 76% of RA sera with a specificity of 96%. Sera showed a remarkable variety in the reactivity pattern towards different **citrulline**-containing peptides. Affinity-purified **antibodies** were shown to be positive in the immunofluorescence-based antiperinuclear factor test, and in the so-called antikeratin **antibody** test, and were reactive towards **filaggrin** extracted from human epidermis. The specific nature of these **antibodies** and the presence of these **antibodies** early in disease, even before other disease manifestations occur, are indicative for a possible role of **citrulline**-containing epitopes in the pathogenesis of RA.
CC **Immunology and Immunochemistry - General; Methods *34502**
Biochemical Studies - General *10060
Bones, Joints, Fasciae, Connective and Adipose Tissue - General; Methods *18001
BC Hominidae 86215
IT Major Concepts
Immune System (Chemical Coordination and Homeostasis)
IT Parts, Structures, & Systems of Organisms
serum: blood and lymphatics
IT Diseases
rheumatoid arthritis: connective tissue disease, immune system disease, joint disease
IT Chemicals & Biochemicals
antikeratin **antibodies**; antiperinuclear factor; autoantigens; **citrulline**; **filaggrin**; **rheumatoid arthritis**-specific **autoantibodies**; **rheumatoid** factor
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae): patient
ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates
RN **372-75-8 (CITRULLINE)**

L100 ANSWER 11 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1997:204698 BIOSIS
DN PREV199799503901
TI Normal human epidermal keratinocytes express in vitro specific molecular forms of (pro)**filaggrin** recognized by **rheumatoid arthritis**-associated **antifilaggrin autoantibodies**.
AU Girbal-Neuhauser, Elisabeth; Montezin, Martine; Croute, Francoise; Sebbag, Mireille; Simon, Michel; Durieux, Jean-Jacques; Serre, Guy (1)
CS (1) Lab. Biologie Cellulaire, C.H.U. Purpan, Place du Dr. Baylac, 31059 Toulouse cedex France
SO Molecular Medicine (New York), (1997) Vol. 3, No. 2, pp. 145-156. ISSN: 1076-1551.
DT Article
LA English
AB Background: The so-called antikeratin **antibodies** and the antiperinuclear factor are the most specific serological markers of **rheumatoid arthritis** (RA). They were recently shown to be largely the same **autoantibodies** and to recognize human epidermal **filaggrins** and **profilaggrin**-related proteins of buccal epithelial cells (collectively referred to as (pro)

filaggrin). Materials and Methods: To further characterize the target antigens, we investigated their expression by normal human epidermal keratinocytes cultured in differentiating conditions, using immunofluorescence and immunoblotting with RA sera and three different monoclonal **antibodies** to (pro)**filaggrin**. Results: On the cornified, stratified epithelial sheets obtained in vitro, RA sera with anti(pro)**filaggrin autoantibodies** (AFA) produced granular staining of the stratum granulosum and diffuse staining of the stratum corneum. The antigens recognized by RA sera strictly colocalized with (pro)**filaggrin** in keratohyalin granules. Following sequential extraction of the proteins from the epithelial sheets, the RA sera and the three monoclonal **antibodies** to (pro) **filaggrin**, recognized a series of low-salt-soluble molecules, including a neutral/acidic isoform of **filaggrin** and several proteins with sizes and pI intermediates between this isoform and **profilaggrin**. They also recognized urea-soluble high-molecular-weight **profilaggrin**-related molecules. Conclusions: These results show that in vitro epidermal keratinocytes express various molecular forms of (pro) **filaggrin** that bear epitopes targeted by AFA of RA sera, and that some of these are absent from epidermis. Moreover, these epitopes, which are present on the keratohyalin granules of buccal epithelial cells but not on those of epidermal cells, are present on the granules of the cultured keratinocytes. This work completes the molecular characterization of the proteins targeted by AFA.

CC Cytology and Cytochemistry - Human *02508
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biochemical Studies - Carbohydrates 10068
Biophysics - Molecular Properties and Macromolecules 10506
Metabolism - Carbohydrates *13004
Metabolism - Proteins, Peptides and Amino Acids *13012
Bones, Joints, Fasciae, Connective and Adipose Tissue - Pathology *18006
Integumentary System - Physiology and Biochemistry *18504
Tissue Culture, Apparatus, Methods and Media 32500
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508

BC Hominidae *86215

IT Major Concepts
Cell Biology; Clinical Immunology (Human Medicine, Medical Sciences); Integumentary System (Chemical Coordination and Homeostasis); Metabolism; Skeletal System (Movement and Support)

IT Miscellaneous Descriptors
CONNECTIVE TISSUE DISEASE; IMMUNE SYSTEM; IMMUNE SYSTEM DISEASE; IN-VITRO SPECIFIC MOLECULAR FORM EXPRESSION; INTEGUMENTARY SYSTEM; JOINT DISEASE; NORMAL EPIDERMAL KERATINOCYTES; PATIENT; **PROFILAGGRIN**; **RHEUMATOID ARTHRITIS**; **RHEUMATOID ARTHRITIS**-ASSOCIATED **ANTIFILAGGRIN AUTOANTIBODY** RECOGNITION

ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
human (Hominidae)

ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates

L100 ANSWER 12 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1997:139836 BIOSIS
DN PREV199799439039
TI **Antibodies** to **filaggrin** are not equally prevalent in all populations of patients with **rheumatoid arthritis** (RA.
AU Slack, S. L.; Mannik, M.; Dale, B. A.
CS Univ. Washington, Seattle, WA USA
SO Journal of Investigative Medicine, (1997) Vol. 45, No. 1, pp. 121A.
Meeting Info.: Meeting of the American Federation for Medical Research,

Western Regional Carmel, California, USA February 5-8, 1997
ISSN: 1081-5589.
DT Conference; Abstract
LA English
CC General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biochemical Studies - Carbohydrates 10068
Bones, Joints, Fasciae, Connective and Adipose Tissue - Pathology *18006
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508
BC Hominidae *86215
IT Major Concepts
Clinical Immunology (Human Medicine, Medical Sciences); Skeletal System (Movement and Support)
IT Miscellaneous Descriptors
ANTIBODIES; CLINICAL IMMUNOLOGY; CONNECTIVE TISSUE DISEASE; **FILAGGRIN**; IMMUNE SYSTEM DISEASE; JOINT DISEASE; ORTHOPEDICS; PATIENT; **RHEUMATOID ARTHRITIS**
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates

L100 ANSWER 13 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1997:134901 BIOSIS
DN PREV199799434104
TI Perinuclear factor (**profilaggrin**) **autoantibodies**.
AU Youinou, Pierre (1); Le Goff, Paul; Maran, Raya
CS (1) Lab. Immunol., Centre Hosp. Regional et Univ., Brest Cedex France
SO Peter, J. B. [Editor]; Shoenfeld, Y. [Editor]. (1996) pp. 618-623.
Autoantibodies.
Publisher: Elsevier Science Publishers B.V. PO Box 211, Sara Burgerhartstraat 25, 1000 AE Amsterdam, Netherlands.
ISBN: 0-444-82383-2.
DT Book
LA English
CC General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biochemical Studies - Carbohydrates *10068
Pathology, General and Miscellaneous - Diagnostic *12504
Endocrine System - General *17002
Bones, Joints, Fasciae, Connective and Adipose Tissue - Pathology *18006
Immunology and Immunochemistry - General; Methods *34502
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508
BC Hominidae *86215
IT Major Concepts
Biochemistry and Molecular Biophysics; Clinical Immunology (Human Medicine, Medical Sciences); Endocrine System (Chemical Coordination and Homeostasis); Immune System (Chemical Coordination and Homeostasis); Pathology; Skeletal System (Movement and Support)
IT Miscellaneous Descriptors
CONNECTIVE TISSUE DISEASE; DIAGNOSTIC METHOD; ELISA; IMMUNE SYSTEM; IMMUNE SYSTEM DISEASE; JOINT DISEASE; PERINUCLEAR FACTOR; PERINUCLEAR FACTOR **AUTOANTIBODIES**; **PROFILAGGRIN**; **RHEUMATOID ARTHRITIS**
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)

ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates

L100 ANSWER 14 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1997:134852 BIOSIS
DN PREV199799434055
TI **Filaggrin** (keratin) **autoantibodies**.
AU **Serre, Guy; Vincent, Christian**
CS Dep. Biol. and Pathol. Cell, Purpan Med. Sch., Univ. Toulouse, 31059 Toulouse Cedex France
SO Peter, J. B. [Editor]; Shoenfeld, Y. [Editor]. (1996) pp. 271-276. Autoantibodies.
Publisher: Elsevier Science Publishers B.V. PO Box 211, Sara Burgerhartstraat 25, 1000 AE Amsterdam, Netherlands.
ISBN: 0-444-82383-2.
DT **Book**
LA English
CC General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biochemical Studies - Carbohydrates *10068
Biophysics - Molecular Properties and Macromolecules *10506
Endocrine System - General *17002
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508
BC Hominidae *86215
IT Major Concepts
Biochemistry and Molecular Biophysics; Clinical Immunology (Human Medicine, Medical Sciences); Endocrine System (Chemical Coordination and Homeostasis)
IT Chemicals & Biochemicals
KERATIN
IT Miscellaneous Descriptors
(PRO)**FILAGGRIN**-RELATED PROTEINS; ANTIPERINUCLEAR FACTOR; **FILAGGRIN; FILAGGRIN AUTOANTIBODIES**; IMMUNE SYSTEM; KERATIN **AUTOANTIBODIES; RHEUMATOID** FACTOR
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates
RN 169799-44-4 (KERATIN)

L100 ANSWER 15 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1997:97993 BIOSIS
DN PREV199799397196
TI Evidence that peptidylarginine deiminase functions as an antichaperonin.
AU Tarcsa, E. (1); Marekov, L. N. (1); Mei, G.; Melino, G.; Steinert, P. M. (1)
CS (1) Lab. Skin Biol., NIAMS, NIH, Bethesda, MD 20892 USA
SO Molecular Biology of the Cell, (1996) Vol. 7, No. SUPPL., pp. 635A.
Meeting Info.: Annual Meeting of the 6th International Congress on Cell Biology and the 36th American Society for Cell Biology San Francisco, California, USA December 7-11, 1996
ISSN: 1059-1524.
DT Conference; Abstract; Conference
LA English
CC General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520
Biochemical Studies - General *10060
Biophysics - General Biophysical Studies *10502
Enzymes - General and Comparative Studies; Coenzymes *10802
BC Muridae *86375
IT Major Concepts
Biochemistry and Molecular Biophysics; Enzymology (Biochemistry and

Molecular Biophysics)
IT Chemicals & Biochemicals
PEPTIDYLARGININE DEIMINASE; **ARGININE**; **CITRULLINE**
IT Miscellaneous Descriptors
ANALYTICAL METHOD; ANTI-CHAPERONIN ACTIVITY; **ARGININE** TO **CITRULLINE** CONVERSION; CIRCULAR DICHROISM SPECTROSCOPY; ENZYMOLOGY; **FILAGGRIN**; HAIR FOLLICLE CELLS; INTEGUMENTARY SYSTEM; IRREVERSIBLE PROTEIN DENATURANT; PEPTIDYLARGININE DEIMINASE; PROTEIN DESTABILIZATION; PROTEIN STRUCTURE UNFOLDING; TRICHOHYALIN
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
mouse (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman mammals; nonhuman vertebrates; rodents; vertebrates
RN 75536-80-0 (PEPTIDYLARGININE DEIMINASE)
74-79-3 (**ARGININE**)
372-75-8 (**CITRULLINE**)

L100 ANSWER 16 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1997:66433 BIOSIS
DN PREV199799365636
TI Detection of several families of deiminated proteins derived from **filaggrin** and keratins in guinea pig skin.
AU Kan, Shuhei; Asaga, Hiroaki (1); Senshu, Tatsuo
CS (1) Dep. Cell Chem., Tokyo Metropolitan Inst. Gerontol, Itabashi-ku, Tokyo 173 Japan
SO Zoological Science (Tokyo), (1996) Vol. 13, No. 5, pp. 673-678. ISSN: 0289-0003.
DT Article
LA English
AB Structural proteins in the mammalian epidermis contain **citrulline** residues generated by enzymatic deimination of **arginine** residues. We analyzed deiminated proteins solubilized from sequentially stripped layers of guinea pig epidermis. Deiminated proteins were localized in the granular and cornified layers. Those in the inner layer enriched with granular cells were resolved into numerous components by two-dimensional gel electrophoresis. An arc-shaped high-molecular-weight smear and two series of charged isomers among them coincided with **filaggrin** immunoreactivity. Several groups of **filaggrin** -negative spots appeared to be generated by further deimination and proteolysis of these **filaggrins**. Deiminated protein spots co-migrating with type II and type I keratins were also detected. Deiminated **filaggrins** and their further processed derivatives disappeared in the outer layer, while deiminated keratins persisted. These data suggested that **filaggrin** as well as **profilaggrin** were deiminated during the posttranslational processing in guinea pig skin, and that some keratins were deiminated preferentially during the cornification of epidermis. Possible biological significance of protein deimination in guinea pig skin was discussed in comparison with our recent finding on deiminated proteins in rat skin.
CC Cytology and Cytochemistry - Animal *02506
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - Molecular Properties and Macromolecules *10506
Integumentary System - Physiology and Biochemistry *18504
BC Caviidae *86300
IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; Integumentary System (Chemical Coordination and Homeostasis)
IT Chemicals & Biochemicals
KERATINS
IT Miscellaneous Descriptors
CORNIFICATION; EPIDERMIS; **FILAGGRIN**; GRANULAR CELL; INTEGUMENTARY SYSTEM; **PROFILAGGRIN**; PROTEIN DEIMINATION; TYPE I KERATIN; TYPE II KERATIN

ORGN Super Taxa
Caviidae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
guinea-pig (Caviidae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman mammals; nonhuman vertebrates; rodents; vertebrates
RN 169799-44-4 (KERATINS)

L100 ANSWER 17 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1997:17731 BIOSIS
DN PREV199799316934
TI Protein unfolding by peptidylarginine deiminase. Substrate specificity and structural relationships of the natural substrates trichohyalin and **filaggrin**.
AU Tarcsa, Edit; Marekov, Lyuben N.; Mei, Giampiero; Melino, Gerrry; Lee, Seung-Chul; Steinert, Peter M. (1)
CS (1) Natl. Inst. Health, Bldg. 6, Rm. 425, 9000 Rockville Pike, Bethesda, MD 20892-2755 USA
SO Journal of Biological Chemistry, (1996) Vol. 271, No. 48, pp. 30709-30716. ISSN: 0021-9258.
DT Article
LA English
AB Peptidylarginine deiminases, which are commonly found in mammalian cells, catalyze the deimination of protein-bound **arginine** residues to **citrullines**. However, very little is known about their substrate requirements and the significance or consequences of this postsynthetic modification. We have explored this reaction in vitro with two known substrates **filaggrin** and trichohyalin. First, the degree and rate of modification of **arginines** to **citrullines** directly correlates with the structural order of the substrate. In **filaggrin**, which has little structural order, the reaction proceeded rapidly to gt 95% completion. However, in the highly alpha-helical protein trichohyalin, the reaction proceeded slowly to about 25% and could be forced to a maximum of about 65%. Second, the rate and degree of modification depends on the sequence location of the target **arginines**. Third, we show by gel electrophoresis, circular dichroism, and fluorescence spectroscopy that the reaction interferes with organized protein structure: the net formation of gtoreq 10% **citrulline** results in protein denaturation. Cyanate modification of the lysines in model alpha-helix-rich proteins to homocitrullines also results in loss of organized structure. These data suggest that the ureido group on the **citrulline** formed by the peptidylarginine deiminase enzyme modification functions to unfold proteins due to decrease in net charge, loss of potential ionic bonds, and interference with H bonds.
CC Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - Molecular Properties and Macromolecules *10506
Enzymes - Chemical and Physical *10806
IT Major Concepts
Biochemistry and Molecular Biophysics; Enzymology (Biochemistry and Molecular Biophysics)
IT Chemicals & Biochemicals
PEPTIDYLARGININE DEIMINASE
IT Sequence Data
amino acid sequence; molecular sequence data
IT Miscellaneous Descriptors
EC 3.5.3.15; ENZYMOLOGY; **FILAGGRIN**; MOLECULAR STRUCTURE; PEPTIDYLARGININE DEIMINASE; PROTEIN UNFOLDING; SUBSTRATE SPECIFICITY; TRICHOHYALIN
RN 75536-80-0 (PEPTIDYLARGININE DEIMINASE)

L100 ANSWER 18 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1996:485441 BIOSIS
DN PREV199699200697
TI Preferential deimination of keratin K1 and **filaggrin** during the terminal differentiation of human epidermis.

AU Senshu, Tatsuo (1); Kan, Shuhei; Ogawa, Hideoki; Manabe, Motomu; Asaga, Hiroaki
CS (1) Dep. Cell Chem., Tokyo Metropolitan Inst. Gerontol., Tokyo 173 Japan
SO Biochemical and Biophysical Research Communications, (1996) Vol. 225, No. 3, pp. 712-719.
ISSN: 0006-291X.
DT Article
LA English
AB The upper layers of mammalian epidermis contain **citrulline** -containing proteins formed by enzymatic deimination of **arginine** residues. To study the role of protein deimination in epidermal differentiation, we identified deiminated proteins extracted from human epidermis. Major deiminated proteins were identified as partially degraded keratin K1, while those from keratin K10 and a highly heterogeneous mixture of deiminated **filaggrin** isomers were detected as minor components. Deiminated keratins were recovered in a fraction enriched with keratins from the codified layers. The subsequent immunohistochemical study showed that deiminated proteins were localized mainly in the lowermost codified layer, but not in the granular layer. These data suggested that partially degraded/disulfide-cross-linked keratin K1 was preferentially deiminated during the terminal stages of epidermal differentiation. We therefore speculated that the protein deimination might influence the interaction of basic K1 with its acidic partner K10, pre-existent K5/K14 networks or keratin-associated protein **filaggrin**.
CC Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biophysics - Molecular Properties and Macromolecules *10506
Enzymes - Physiological Studies *10808
Metabolism - Proteins, Peptides and Amino Acids *13012
Integumentary System - Physiology and Biochemistry *18504
BC Hominidae *86215
IT Major Concepts
Biochemistry and Molecular Biophysics; Enzymology (Biochemistry and Molecular Biophysics); Integumentary System (Chemical Coordination and Homeostasis); Metabolism
IT Miscellaneous Descriptors
ENZYMATIC DEIMINATION; EPIDERMAL TERMINAL DIFFERENTIATION; **FILAGGRIN**; INTEGUMENTARY SYSTEM; KERATIN K1
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates

L100 ANSWER 19 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1996:238324 BIOSIS
DN PREV199698786453
TI Predictors of joint damage in **rheumatoid arthritis**.
AU Wollheim, Frank A.
CS Dep. Rheumatology, Lund Univ. Hosp., S-221 85 Lund Sweden
SO APMIS, (1996) Vol. 104, No. 2, pp. 81-93.
ISSN: 0903-4641.
DT General Review
LA English
AB **Rheumatoid arthritis** (RA) is the dominant form of destructive chronic **arthritis** with the potential to cause substantial disability and permanent functional impairment. The final extent and progression rate with time, however, varies markedly. In order to study effects of intervention and to support early aggressive and atoxic therapy in selected cases, predictive disease markers are needed. Recent advances regarding joint tissue composition and pathophysiology have defined a number of biological marker candidates which need to be explored for possible prognostic information. Some markers are characteristic for RA, such as **rheumatoid** factors and certain **autoantibodies**, which although they are more prevalent among

patients with aggressive disease are not sensitive as predictors in early disease. Genetic susceptibility markers have been claimed to be good predictors of persisting **arthritis** in early synovitis clinics, but their role as severity markers in established disease is limited. Unspecific markers of inflammation, notably ESR or CRP when persistently elevated, are useful to monitor disease course and newer markers need to document their superiority over these. Another group of markers are attractive because of enriched or exclusive occurrence in joint tissue, and altered metabolism in joint disease. Thus, collagen type III propeptides, hyaluronates, and neopterin originating in the synovium could be useful, and, in particular, hyaluronate levels indeed do provide some predictive information. Highly tissue-specific cartilage metabolites include aggrecan fragments, collagen II fragments, cartilage oligomeric matrix protein (COMP) and the extraarticular cartilage matrix protein (CMP). When used alone or in combination in early disease some information can be obtained which may in the future facilitate prognostication. Bone metabolism can be monitored and there are different markers for synthesis and resorption. Meanwhile, whilst the new markers are essential research tools, their routine clinical usefulness remains to be proven.

CC Genetics and Cytogenetics - Human *03508
Biochemical Studies - General 10060
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biochemical Studies - Carbohydrates 10068
Pathology, General and Miscellaneous - Inflammation and Inflammatory Disease *12508
Metabolism - General Metabolism; Metabolic Pathways *13002
Bones, Joints, Fasciae, Connective and Adipose Tissue - Physiology and Biochemistry *18004
Bones, Joints, Fasciae, Connective and Adipose Tissue - Pathology *18006
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508

BC Hominidae *86215

IT Major Concepts
Clinical Immunology (Human Medicine, Medical Sciences); Genetics; Metabolism; Pathology; Skeletal System (Movement and Support)

IT Chemicals & Biochemicals
HYALURONATE; NEOPTERIN

IT Miscellaneous Descriptors
ACUTE PHASE PROTEIN; AGGRECAN FRAGMENT; ANTI-**FILAGGRIN**; ANTI-RA-33; BONE METABOLISM; CARTILAGE OLIGOMERIC MATRIX PROTEIN; COLLAGEN II FRAGMENT; COLLAGEN TYPE III PROPEPTIDE; EXTRAARTICULAR CARTILAGE MATRIX PROTEIN; GENETIC MARKER; HYALURONATE; NEOPTERIN; **RHEUMATOID** FACTOR; SOLUBLE ADHESION MOLECULE; SYNOVIUM

ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
human (Hominidae)

ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates

RN 9004-61-9 (HYALURONATE)
670-65-5Q (NEOPTERIN)
2009-64-5Q (NEOPTERIN)

L100 ANSWER 20 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1996:220669 BIOSIS
DN PREV199698776798
TI Characterization of an immortalized cell line from a patient with epidermolytic hyperkeratosis.
AU Chipev, Constantin C.; Steinert, Peter M. (1); Woodworth, Craig D.
CS (1) Building 6, Room 425, NIAMS/NIH, Bethesda, MD 20892-2755 USA
SO Journal of Investigative Dermatology, (1996) Vol. 106, No. 3, pp. 385-390. ISSN: 0022-202X.
DT Article
LA English
AB The most frequent mutation that causes the autosomal dominant skin disease

epidermolytic hyperkeratosis (EHK) is an **arginine** to histidine substitution at position 10 in the IA segment of the rod domain of keratin 10. As an initial step toward developing a strategy for treating EHK, a cell line, EH18-1, was established after keratinocytes derived from an EHK patient with this mutation were immortalized by a recombinant retrovirus encoding the E6 and E7 genes of human papillomavirus type 18. EH18-1 cells synthesize considerable amounts of keratin 10 mRNA and protein when maintained in either submerged cultures or in organotypic cultures. When grown in organotypic culture, EH18-1 cells form multiple layers and express keratin 10 and **filaggrin** predominantly in the upper layers. Thus, the EH18-1 cell line exhibits several morphological and biochemical markers of terminal epidermal differentiation. A semiquantitative reverse transcriptase polymerase chain reaction assay for keratin 10 mRNA was developed to distinguish between expression of the normal and the mutant alleles. The EH18-1 keratinocyte cell line will be useful in developing protocols for gene therapy of EHK that may be monitored by reverse transcriptase polymerase chain reaction of either allele.

CC Cytology and Cytochemistry - Human *02508
Genetics and Cytogenetics - Human *03508
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines 10062
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Replication, Transcription, Translation *10300
Anatomy and Histology, General and Comparative - Microscopic and Ultramicroscopic Anatomy *11108
Metabolism - Proteins, Peptides and Amino Acids *13012
Metabolism - Nucleic Acids, Purines and Pyrimidines *13014
Integumentary System - Pathology *18506
Developmental Biology - Embryology - Morphogenesis, General *25508
Tissue Culture, Apparatus, Methods and Media *32500
Virology - Animal Host Viruses *33506

BC Papovaviridae 02616
Hominidae *86215

IT Major Concepts
Cell Biology; Dermatology (Human Medicine, Medical Sciences); Development; Genetics; Metabolism; Methods and Techniques; Microbiology; Molecular Genetics (Biochemistry and Molecular Biophysics); Morphology

IT Miscellaneous Descriptors
CELL MORPHOLOGY; EH18-1 CELL LINE; **FILAGGRIN**; GENE EXPRESSION; KERATIN 10; KERATINOCYTE; MESSENGER RNA; MUTATION; ORGANOTYPIC CULTURE; SUBMERGED CULTURE; TERMINAL DIFFERENTIATION

ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia; Papovaviridae: Viruses

ORGN Organism Name
human papillomavirus type 18 (Papovaviridae); Hominidae (Hominidae)

ORGN Organism Superterms
animals; chordates; humans; mammals; microorganisms; primates; vertebrates; viruses

L100 ANSWER 21 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1996:108161 BIOSIS
DN PREV199698680296
TI Trends in **rheumatoid arthritis** research.
AU Emilie, Dominique; Russo-Marie, Francoise (1)
CS (1) INSERM U. 322, 22 rue Mechain, 75014 Paris France
SO M-S (Medecine Sciences), (1995) Vol. 11, No. 11, pp. 1577-1580. ISSN: 0767-0974.
DT Article
LA French

CC Cytology and Cytochemistry - Human *02508
Genetics and Cytogenetics - Human *03508
Biochemical Studies - General 10060
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines 10062
Biochemical Studies - Vitamins 10063

Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biochemical Studies - Lipids 10066
Biochemical Studies - Carbohydrates 10068
Biophysics - Membrane Phenomena *10508
Enzymes - Physiological Studies *10808
Pathology, General and Miscellaneous - Inflammation and Inflammatory Disease *12508
Metabolism - Proteins, Peptides and Amino Acids *13012
Blood, Blood-Forming Organs and Body Fluids - Blood Cell Studies *15004
Blood, Blood-Forming Organs and Body Fluids - Lymphatic Tissue and Reticuloendothelial System *15008
Urinary System and External Secretions - Pathology *15506
Endocrine System - General *17002
Muscle - Pathology *17506
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508

BC Gram-Positive Cocci 07700
Hominidae 86215
Muridae *86375

IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Cell Biology; Clinical Immunology (Human Medicine, Medical Sciences); Endocrine System (Chemical Coordination and Homeostasis); Enzymology (Biochemistry and Molecular Biophysics); Genetics; Membranes (Cell Biology); Metabolism; Muscular System (Movement and Support); Pathology; Urology (Human Medicine, Medical Sciences)

IT Chemicals & Biochemicals
METHOTREXATE; KETOPROFEN; MYCOPHENOLIC ACID; UDP-GLUCURONOSYLTRANSFERASE; PROTEASE; PHOSPHOLIPASE A2

IT Miscellaneous Descriptors
ANKYLOSING **SPONDYLARTHRITIS**; ANNEXIN; **AUTOANTIBODY**; AUTOIMMUNE RESPONSE; BETA-2-MICROGLOBULIN; ENDOTHELIAL CELL; **FILAGGRIN**; GENE EXPRESSION; GENE TRANSFER; GENETIC ANOMALY; HLA SYSTEM; HLA-DRB GENE; INTERLEUKIN; INTERLEUKIN-10; ISOFORM EXPRESSION; KETOPROFEN; METHOTREXATE; MIC-A GENE; MYCOPHENOLIC ACID; PHOSPHOLIPASE A2; PROTEASE; SYSTEMIC LUPUS ERYTHEMATOSUS; T-LYMPHOCYTE ANTIGEN RECEPTOR; TREATMENT; TUMOR NECROSIS FACTOR; UDP-GLUCURONOSYLTRANSFERASE

ORGN Super Taxa
Gram-Positive Cocci: Eubacteria, Bacteria; Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia; Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
gram-positive cocci (Gram-Positive Cocci); human (Hominidae); mouse (Muridae); rat (Muridae); Streptococcus mutans (Gram-Positive Cocci)

ORGN Organism Superterms
animals; bacteria; chordates; eubacteria; humans; mammals; microorganisms; nonhuman mammals; nonhuman vertebrates; primates; rodents; vertebrates

RN 59-05-2 (METHOTREXATE)
22071-15-4 (KETOPROFEN)
24280-93-1 (MYCOPHENOLIC ACID)
9030-08-4 (UDP-GLUCURONOSYLTRANSFERASE)
9001-92-7 (PROTEASE)
9001-84-7 (PHOSPHOLIPASE A2)

L100 ANSWER 22 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1995:454484 BIOSIS
DN PREV199598468784
TI Rat epidermal cathepsin L-like proteinase: Purification and some hydrolytic properties toward **filaggrin** and synthetic substrates.
AU Kawada, Akira (1); Hara, Kenji; Hiruma, Masataro; Noguchi, Hiromitsu; Ishibashi, Akira
CS (1) Dep. Dermatol., Natl. Defense Med. Coll., 3-2 Namiki, Tokorozawa, Saitama 359 Japan
SO Journal of Biochemistry (Tokyo), (1995) Vol. 118, No. 2, pp. 332-337. ISSN: 0021-924X.

DT Article
LA English
AB We have purified cathepsin L-like proteinase from rat epidermis, determined its NH-2-terminal amino acid sequence, and investigated its proteolytic activities on an intermediate filament-associated protein **filaggrin** and several synthetic substrates. The amino acid sequence of its NH,-terminus was determined to be Val-Pro-Asn-Ser-Leu-Asp-Trp-**Arg**-Glu-Lys-Gly-Tyr-Val-Thr-Pro-, which differed from that of rat cathepsin L and was not found in the amino acid sequence data bank. The enzyme consisted of a single-chain form with M, 30,000. Its hydrolytic properties toward synthetic substrates were similar to those of cathepsin L in other tissues. The enzyme effectively proteolyzed rat epidermal **filaggrin** into small fragments at pH 4.0-6.0 and was inhibited by a specific cysteine proteinase inhibitor, N-(N-(L-3-trans-carboxyoxirane-2-carbonyl)L-leucyl)-agmatin. However, cathepsins D and E from rat epidermis did not hydrolyze **filaggrin**. This study demonstrated that **filaggrin** was susceptible to degradation by rat epidermal cathepsin L-like proteinase, suggesting that this proteolytic activity may have relevance to skin differentiation, in which acid proteases are thought to participate.
CC Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Enzymes - Physiological Studies *10808
Metabolism - Proteins, Peptides and Amino Acids *13012
Integumentary System - Physiology and Biochemistry *18504
BC Muridae *86375
IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics); Integumentary System (Chemical Coordination and Homeostasis); Metabolism
IT Chemicals & Biochemicals
CATHEPSIN L; PROTEINASE; EC 3.4.22.15
IT Miscellaneous Descriptors
EC 3.4.22.15; KERATINIZATION
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Muridae (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman vertebrates; nonhuman mammals; rodents; vertebrates
RN 60616-82-2 (CATHEPSIN L)
9001-92-7 (PROTEINASE)
60616-82-2 (EC 3.4.22.15)

L100 ANSWER 23 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1995:438683 BIOSIS
DN PREV199598452983
TI Detection of deiminated proteins in rat skin: Probing with a monospecific antibody after modification of **citrulline** residues.
AU Senshu, Tatsuo (1); Akiyama, Kyoichi; Kan, Shuhei; Asaga, Hiroaki; Ishigami, Akihito; Manabe, Motomu
CS (1) Dep. Cell Chem., Tokyo Metropolitan Inst. Gerontol., 35-2 Sakae-cho, Itabashi-ku, Tokyo 173 Japan
SO Journal of Investigative Dermatology, (1995) Vol. 105, No. 2, pp. 163-169. ISSN: 0022-202X.
DT Article
LA English
AB We performed a systematic study on deiminated proteins present in rat epidermis. Proteins extracted from various epidermal samples were resolved by either one- or two-dimensional gel electrophoresis and Western blotted to nitrocellulose membranes. Deiminated proteins were detected by modification of **citrulline** residues followed by probing with an anti-modified **citrulline** monospecific antibody. The cornified layer of adult plantar skin gave multiple series of isoelectric variants, most of which were found to be differentially deiminated type II keratins (60 kDa, and 67 kDa or above). The whole epidermis of 5-day-old rat back skin showed isoelectric variants of 60-kDa keratin as major deiminated

components, and deiminated 55-kDa keratin and deiminated **filaggrin** as minor spots. In addition, we found highly deiminated proteins (200-220 kDa) thought to be derived from trichohyalin. The immunoreactivity of deiminated proteins was mainly localized in the granular and cornified layers of epidermis. Co-localization of deiminated **filaggrin** and keratins in the granular layer suggests the possible role of protein deimination during the terminal stage of epidermal differentiation.

CC Cytology and Cytochemistry - Animal *02506
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biochemical Studies - Carbohydrates 10068
Anatomy and Histology, General and Comparative - Microscopic and Ultramicroscopic Anatomy *11108
Integumentary System - Anatomy *18502
Integumentary System - Physiology and Biochemistry *18504
Developmental Biology - Embryology - Morphogenesis, General *25508

BC Muridae *86375

IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; Development; Integumentary System (Chemical Coordination and Homeostasis); Morphology

IT Chemicals & Biochemicals
CITRULLINE

IT Miscellaneous Descriptors
CORNIFIED LAYER; DERMATOLOGY; **FILAGGRIN**; GRANULAR LAYER; PHOTOMICROGRAPH; TERMINAL DIFFERENTIATION STAGE; TRICHOHYALIN; TYPE II KERATIN

ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
Muridae (Muridae)

ORGN Organism Superterms
animals; chordates; mammals; nonhuman vertebrates; nonhuman mammals; rodents; vertebrates

RN **372-75-8 (CITRULLINE)**

L100 ANSWER 24 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1995:438392 BIOSIS
DN PREV199598452692
TI The antiperinuclear factor and antikeratin **antibody** systems.
AU Youinou, Pierre (1); Serre, Guy
CS (1) Lab. Immunol., Brest Univ. Med. Sch. Hosp., BP 824, F-29609 Brest Cedex France
SO International Archives of Allergy and Immunology, (1995) Vol. 107, No. 4, pp. 508-518.
ISSN: 1018-2438.
DT General Review
LA English
AB Antiperinuclear factor (APF) and antikeratin **antibody** (AKA) have long been known to be associated with **rheumatoid arthritis**. Human buccal mucosa epithelial cells have hitherto been required as the substrate in the APF test, while AKAs are detected on rat esophagus sections, using an indirect immunofluorescence technique. These two **autoantibodies** proved to be interrelated. Cytoplasmic inclusions in buccal cells have presumptively been termed keratohyalin granules and the APF target antigen colocalizes exactly with that of **antiprofilaggrin antibody** within the perinuclear organelles. The latter protein has convincingly been identified as the genuine specificity of the so-called AKA.

CC Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biochemical Studies - Carbohydrates *10068
Pathology, General and Miscellaneous - Inflammation and Inflammatory Disease *12508
Bones, Joints, Fasciae, Connective and Adipose Tissue - Pathology *18006
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508

BC Hominidae *86215
IT Major Concepts
Biochemistry and Molecular Biophysics; Clinical Immunology (Human Medicine, Medical Sciences); Pathology; Skeletal System (Movement and Support)
IT Miscellaneous Descriptors
RHEUMATOID ARTHRITIS
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates

L100 ANSWER 25 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1995:393104 BIOSIS
DN PREV199598407404
TI Proliferation and interferon-gamma receptor expression in psoriatic and healthy keratinocytes are influenced by interactions between keratinocytes and fibroblasts in a skin equivalent model.
AU Fransson, Jessica (1); Emilson, Axel; Scheynius, Annika; Hammar, Hans
CS (1) Dep. Dermatol., Karolinska Hospital, S-171 76 Stockholm Sweden
SO Archives of Dermatological Research, (1995) Vol. 287, No. 6, pp. 517-523. ISSN: 0340-3696.
DT Article
LA English
AB Epidermal-dermal interactions were studied in a skin equivalent model. Six combinations of keratinocytes and fibroblasts from healthy and psoriatic skin were used. TPA (12-O-tetradecanoylphorbol-13-acetate) was used to determine whether the expression of the IFN-gamma receptors in keratinocytes was related to epidermal differentiation and proliferation. These phenomena were assessed by immunohistochemistry. In all epidermal outgrowths, the epidermal growth factor receptor was expressed throughout the epidermis, cytokeratin 16 suprabasally, and **filaggrin** and involucrin in its superficial part. The IFN-gamma receptor was expressed throughout the epidermis, but was unevenly distributed. The expression of the IFN-gamma receptor was quantified by confocal laser scanning microscopy both in the whole of epidermis and in areas with the strongest intensity. The total amount varied to a minor degree in the epidermal outgrowths of different origins and was unaffected by TPA. In high-intensity areas interactions between keratinocytes and fibroblasts did influence the amount of IFN-gamma receptor expression and TPA decreased the expression by 13%. There was no correlation between the proliferation rate and the expression of the IFN-gamma receptor. Psoriatic and healthy keratinocytes were equally well differentiated in the skin equivalents. The interferon-gamma receptor was similarly expressed under these conditions. The growth rate, assessed by Ki-67-positive nuclei in the basal layer, was highest in healthy keratinocytes. Keratinocytes from psoriatic lesions increased their growth rate when cocultured with psoriatic fibroblasts compared with normal ones, indicating that fibroblasts may be of importance for epidermal hyperproliferation in psoriatic lesions.
CC Microscopy Techniques - General and Special Techniques 01052
Microscopy Techniques - Histology and Histochemistry 01056
Cytology and Cytochemistry - Human *02508
Radiation - Radiation and Isotope Techniques 06504
Biophysics - Molecular Properties and Macromolecules *10506
Biophysics - Membrane Phenomena *10508
Anatomy and Histology, General and Comparative - Microscopic and Ultramicroscopic Anatomy *11108
Pathology, General and Miscellaneous - Inflammation and Inflammatory Disease *12508
Bones, Joints, Fasciae, Connective and Adipose Tissue - Anatomy *18002
Integumentary System - Anatomy *18502
Integumentary System - Pathology *18506

Developmental Biology - Embryology - Morphogenesis, General *25508
Immunology and Immunochemistry - General; Methods *34502
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508
BC Hominidae *86215
IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; Clinical Immunology (Human Medicine, Medical Sciences); Dermatology (Human Medicine, Medical Sciences); Development; Immune System (Chemical Coordination and Homeostasis); Integumentary System (Chemical Coordination and Homeostasis); Membranes (Cell Biology); Morphology; Pathology; Skeletal System (Movement and Support)
IT Miscellaneous Descriptors
CONFOCAL LASER SCANNING MICROSCOPY; EPIDERMAL DIFFERENTIATION; EPIDERMAL-DERMAL INTERACTION; IMMUNOHISTOCHEMISTRY; INTERFERON-GAMMA RECEPTOR
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates

L100 ANSWER 26 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1995:373464 BIOSIS
DN PREV199598387764
TI Prenatal diagnosis of skin disease.
AU Brenner, S. (1); Kurjak, A.; Jurkovic, D.; Kobayasi, T.; Brandsen, R. E.; Matż, H.; Marton, U.
CS (1) Dep. Dermatol., Tel Aviv Med. Cent., Tel Aviv Israel
SO Kurjak, A. [Editor]; Chervenak, F. A. [Editor]. (1994) pp. 359-377. The fetus as a patient.
Publisher: Parthenon Publishing Group Ltd. Casterton Hall, LA6 2LA Carnforth, England, UK.
ISBN: 1-85070-558-5.
DT Book
LA English
CC Genetics and Cytogenetics - Human *03508
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Enzymes - Methods 10804
Pathology, General and Miscellaneous - Diagnostic *12504
Metabolism - Metabolic Disorders *13020
Reproductive System - General; Methods 16501
Reproductive System - Physiology and Biochemistry *16504
Reproductive System - Pathology *16506
Bones, Joints, Fasciae, Connective and Adipose Tissue - Pathology *18006
Integumentary System - Pathology *18506
Developmental Biology - Embryology - General and Descriptive *25502
Developmental Biology - Embryology - Pathological *25503
Developmental Biology - Embryology - Descriptive Teratology and Teratogenesis *25552
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508
BC Hominidae *86215
IT Major Concepts
Clinical Immunology (Human Medicine, Medical Sciences); Dermatology (Human Medicine, Medical Sciences); Development; Genetics; Metabolism; Pathology; Reproductive System (Reproduction); Skeletal System (Movement and Support)
IT Miscellaneous Descriptors
BIOPSY; BOOK CHAPTER; CHROMOSOMAL ABERRATION; CONGENITAL ECTODERMAL DEFECTS; CONNECTIVE TISSUE DISORDERS; ENZYME ASSAY; **FILAGGRIN** ; IMMUNE DISORDERS; KERATIN; METABOLIC DISORDERS; PIGMENTARY DISORDERS; REPRODUCTIVE MEDICINE
ORGN Super Taxa

Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates

L100 ANSWER 27 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1995:345856 BIOSIS
DN PREV199598360156
TI The antiperinuclear factor and the so-called antikeratin **antibodies** are the same **rheumatoid arthritis** -specific **autoantibodies**.
AU Sebbag, Mireille; Simon, Michel; Vincent, Christian; Masson-Bessiere, Christine; Girbal, Elisabeth; Durieux, Jean-Jacques; Serre, Guy (1)
CS (1) Lab. de Biol. Cellulaire, CHU Purpan, Place du Dr. Baylac, 31059 Toulouse Cedex France
SO Journal of Clinical Investigation, (1995) Vol. 95, No. 6, pp. 2672-2679. ISSN: 0021-9738.
DT Article
LA English
AB The so-called antikeratin **antibodies** (AKA) and the antiperinuclear factor (APF) are the most specific serological markers of RA. Using indirect immunofluorescence, AKA label the stratum corneum of various cornified epithelia and APF the keratohyalin granules of human buccal mucosa epithelium. We recently demonstrated that AKA recognize human epidermal **filaggrin**. Here, we report the identification of the major APF antigen as a diffuse protein band of 200-400 kD. This protein is seen to be closely related to human epidermal (pro) **filaggrin** since it was recognized by four **antifilaggrin** mAbs specific for different epitopes, and since the APF titers of RA sera were found to be correlated to their AKA titers and to their immunoblotting reactivities to **filaggrin**. Immunoabsorption of RA sera on purified epidermal **filaggrin** abolished their reactivities to the granules of buccal epithelial cells and to the 200-400-kD antigen. Moreover, **antifilaggrin autoantibodies**, i.e., AKA, affinity purified from RA sera, were shown to immunodetect the 200-400-kD antigen and to stain these granules. These results indicate that AKA and APF are largely the same **autoantibodies**. They recognize human epidermal **filaggrin** and (pro)**filaggrin**-related proteins of buccal epithelial cells. Identification of the epitopes recognized by these **autoantibodies**, which we propose to name **antifilaggrin autoantibodies**, will certainly open new paths of research into the pathophysiology of RA.
CC Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Pathology, General and Miscellaneous - Inflammation and Inflammatory Disease *12508
Bones, Joints, Fasciae, Connective and Adipose Tissue - Pathology *18006
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508
BC Hominidae *86215
IT Major Concepts
Clinical Immunology (Human Medicine, Medical Sciences); Pathology; Skeletal System (Movement and Support)
IT Miscellaneous Descriptors
ANTIFILAGGRIN; AUTOIMMUNITY; **PROFILAGGRIN**
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates

L100 ANSWER 28 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1995:299449 BIOSIS

DN PREV199598313749
TI Rat epidermal cathepsin B: Purification and characterization of proteolytic properties toward **filaggrin** and synthetic substrates.
AU Kawada, Akira (1); Hara, Kenji; Morimoto, Koukichi; Hiruma, Masataro; Ishibashi, Akira
CS (1) Dep. Dermatol., National Defense Med. College, Namiki 3-2, Tokorozawa City, Saitama 359 Japan
SO International Journal of Biochemistry & Cell Biology, (1995) Vol. 27, No. 2, pp. 175-183.
ISSN: 1357-2725.
DT Article
LA English
AB The aim of this study was to purify epidermal cathepsin B from rat skin and investigate its proteolytic activities on **filaggrin** and several synthetic substrates. The molecular weight of purified monomeric cathepsin B was estimated to be 30 kDa by SDS-polyacrylamide gel electrophoresis. The amino acid composition, similar to that of liver cathepsin B, indicated the enzyme to be an acidic protease. The enzyme had strong hydrolytic activity toward N-benzyloxycarbonyl-L-**arginyl**-L-**arginine**-7-amido-4-methylcoumarin (Z-**Arg**-**Arg**-MCA) (152 mU/mg) and N-benzyloxycarbonyl-L-phenylalanyl-L-**arginine**-7-amido-4-methylcoumarin (424 mU/mg), but had no proteolytic activity toward L-**arginine**-7-amido-4-methylcoumarin. The K-m value for Z-**Arg**-**Arg** MCA was 0.34 mM and pH optimum was 5.5. Cathepsin B degraded rat epidermal **filaggrin** into small fragments at pH 4.0 and 5.5, and was inhibited by a specific cysteine proteinase inhibitor, N-(N-(L-3-trans-carboxyoxirane-2-carbonyl)L-leucyl)-agmatin. This study demonstrated that **filaggrin** was susceptible to degradation by cathepsin B. Such an action may have relevance to skin differentiation in which acid proteases are thought to participate.
CC Biochemical Methods - Proteins, Peptides and Amino Acids *10054
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biophysics - General Biophysical Techniques 10504
Enzymes - Physiological Studies *10808
Integumentary System - Physiology and Biochemistry *18504
BC Muridae *86375
IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics); Integumentary System (Chemical Coordination and Homeostasis); Methods and Techniques
IT Chemicals & Biochemicals
CATHEPSIN B; PROTEASE
IT Miscellaneous Descriptors
AMINO ACID COMPOSITION; DIFFERENTIATION; PROTEASE; PURIFICATION METHOD; SDS POLYACRYLAMIDE GEL ELECTROPHORESIS
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Muridae (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman vertebrates; nonhuman mammals; rodents; vertebrates
RN 9047-22-7 (CATHEPSIN B)
9001-92-7 (PROTEASE)

L100 ANSWER 29 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1995:221530 BIOSIS
DN PREV199598235830
TI The **rheumatoid arthritis**-associated **autoantibodies** to **filaggrin** label the fibrous matrix of the cornified cells but not the **profilaggrin**-containing keratohyalin granules in human epidermis.
AU Simon, M.; Vincent, C.; Haftek, M.; Girbal, E.; Sebbag, M.; Gomes-Daudrix, V.; Serre, G. (1)
CS (1) Labortorie de Biologie Cellulaire et Cytologie, CHU Purpan, Place du

Dr Baylac, 31059 Toulouse Cedex France
SO Clinical and Experimental Immunology, (1995) Vol. 100, No. 1, pp. 90-98. ISSN: 0009-9104.
DT Article
LA English
AB Since they were first described, serum IgG **antibodies** to the stratum corneum of rat oesophagus epithelium, highly specific for **rheumatoid arthritis** (RA), have been consensually called antikeratin **antibodies** (AKA). However, we recently demonstrated that they actually recognize three new proteins of rat oesophagus epithelium distinct from cytokeratins, and also human epidermal **filaggrin**. In this work we provided further evidence that AKA and RA-associated anti-**filaggrin autoantibodies** are the same **antibodies**. Moreover, analyzing by indirect immunofluorescence on human skin a large series of 212 well characterized RA sera and anti-**filaggrin autoantibodies** purified from RA sera by affinity chromatography, we demonstrated the specific binding of AKA to the stratum corneum of human epidermis and the absence of any staining of the granular keratinocytcs. This binding was confirmed and the AKA antigen precisely localized in human epidermis by immunoelectron microscopy. The antigen was found to be restricted to the **filaggrin**-containing intracellular fibrous matrix of the corneocytes, up to the desquamating cells. In contrast, MoAbs directed to human **filaggrin** and to **profilaggrin**, its precursor, not only stained the intracellular matrix of the lower corneocytes but also the keratohyalin granules of the granular cells, where **profilaggrin** is stored. These results reinforced by the absence of immunoblotting reactivity of RA sera to **profilaggrin** suggest that the epitopes recognized by AKA are absent from **profilaggrin** . Their identification may provide more insight into the pathogenesis of RA.
CC Microscopy Techniques - General and Special Techniques 01052
Microscopy Techniques - Histology and Histochemistry 01056
Cytology and Cytochemistry - Animal *02506
Radiation - Radiation and Isotope Techniques 06504
Biochemical Methods - Proteins, Peptides and Amino Acids *10054
Biochemical Methods - Carbohydrates *10058
Biochemical Methods - Minerals 10059
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biochemical Studies - Carbohydrates 10068
Biophysics - General Biophysical Techniques 10504
Anatomy and Histology, General and Comparative - Microscopic and Ultramicroscopic Anatomy *11108
Pathology, General and Miscellaneous - Inflammation and Inflammatory Disease *12508
Metabolism - Carbohydrates *13004
Metabolism - Proteins, Peptides and Amino Acids *13012
Digestive System - Anatomy *14002
Blood, Blood-Forming Organs and Body Fluids - Blood and Lymph Studies *15002
Blood, Blood-Forming Organs and Body Fluids - Lymphatic Tissue and Reticuloendothelial System *15008
Bones, Joints, Fasciae, Connective and Adipose Tissue - Pathology *18006
Integumentary System - Anatomy *18502
Integumentary System - Physiology and Biochemistry *18504
Immunology and Immunochemistry - General; Methods *34502
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508
BC Hominidae 86215
Muridae *86375
IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Cell Biology; Clinical Immunology (Human Medicine, Medical Sciences); Digestive System (Ingestion and Assimilation); Immune System (Chemical Coordination and Homeostasis); Integumentary System (Chemical

Coordination and Homeostasis); Metabolism; Methods and Techniques; Morphology; Pathology; Skeletal System (Movement and Support)
IT Miscellaneous Descriptors
AFFINITY PURIFICATION; ANTI-KERATIN **ANTIBODY**; CYTOKERATINS; IMMUNOELECTRON MICROSCOPY; IMMUNOGOLD LABELLING; INDIRECT IMMUNOFLUORESCENCE; PATHOGENESIS; **PROFILAGGRIN** RAT ESOPHAGUS
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia; Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Hominidae (Hominidae); Muridae (Muridae)
ORGN Organism Superterms
animals; chordates; humans; mammals; nonhuman mammals; nonhuman vertebrates; primates; rodents; vertebrates

L100 ANSWER 30 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1994:18453 BIOSIS
DN PREV199497031453
TI Characterisation of the rat oesophagus epithelium antigens defined by the so-called 'antikeratin **antibodies**', specific for **rheumatoid arthritis**.
AU Girbal, Elisabeth; Sebbag, Mireille; Gomes-Daudrix, Veronique; Simon, Michel; Vincent, Christian; Serre, Guy (1)
CS (1) Laboratoire de Biologie Cellulaire, CHU Purpan, Place du Dr. Baylac, 31059 Toulouse Cedex France
SO Annals of the Rheumatic Diseases, (1993) Vol. 52, No. 10, pp. 749-757. ISSN: 0003-4967.
DT Article
LA English
AB Objectives-An attempt was made to characterise the antigens recognised by serum IgG **antibodies** directed to the stratum corneum of rat oesophagus epithelium, the so-called 'antikeratin **antibodies**', which were shown to be highly specific for **rheumatoid arthritis** (RA) and thus to have an actual diagnostic value. Methods-Immunoblotting was performed with RA serum samples on different extracts of rat oesophagus epithelium separated by various monodimensional and two dimensional electrophoreses. Results-Three low-salt-soluble antigens sensitive to proteinase K and, therefore, of protein nature were identified. Two proteins, with apparent molecular masses of 210 and 120-90 kilodaltons, shared isoelectric points ranging from 5.8 to 8.5; the third protein exhibited isoelectric points from 4.5 to 7.2 while its molecular mass ranged from 130 to 60 kilodaltons. Immunoadsorption of RA serum samples onto cytokeratins extracted from the stratum corneum of rat oesophagus epithelium did not change their immunoreactivity towards the three antigenic proteins. Widely used deglycosylation and dephosphorylation methods failed to modify either the electrophoretic migration of the proteins or their immunoreactivity with RA serum samples. Conclusion-The so-called 'antikeratin **antibodies**' do not react with cytokeratins. They specifically recognise three late epithelial differentiation proteins which had not been previously described. These proteins may be related to (pro)**filaggrin**.
CC Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biochemical Studies - Carbohydrates 10068
Pathology, General and Miscellaneous - Diagnostic *12504
Pathology, General and Miscellaneous - Inflammation and Inflammatory Disease *12508
Bones, Joints, Fasciae, Connective and Adipose Tissue - Pathology *18006
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508
BC Muridae *86375
IT Major Concepts
Immune System (Chemical Coordination and Homeostasis); Pathology; Skeletal System (Movement and Support)
IT Miscellaneous Descriptors
DIAGNOSIS; ESOPHAGUS; IMMUNOGLOBULIN G

ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Muridae (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman vertebrates; nonhuman mammals; rodents; vertebrates

L100 ANSWER 31 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1993:523774 BIOSIS
DN PREV199396137181
TI Characterization of protease processing sites during conversion of rat **profilaggrin** to **filaggrin**.
AU Resing, K. A. (1); Johnson, R. S.; Walsh, K. A.
CS (1) Dep. Chem. Biochem., Campus Box 215, Univ. Colorado, Boulder, CO 80309 USA
SO Biochemistry, (1993) Vol. 32, No. 38, pp. 10036-10045.
ISSN: 0006-2960.
DT Article
LA English
AB **Profilaggrin** is an intermediate filament-associated protein of cornified epithelia. It consists of multiple copies of similar **filaggrin** domains joined by peptide linker regions; during terminal differentiation of the epidermis, the linker regions are processed away in a regulated manner. In order to characterize the sites of proteolysis in rat **profilaggrin**, tryptic peptides of **filaggrin** and **profilaggrin** were fractionated by reverse-phase HPLC, and the HPLC fractions were analyzed by nebulization-assisted electrospray ionization mass spectrometry. Peptide sequences were confirmed or corrected by tandem mass spectrometry; in several cases, this was achieved by collisional activation of multiply charged precursor ions of peptides exceeding 3 kDa in mass. The tryptic peptides accounted for all of the sequence predicted by a partial cDNA sequence, with the exception of six **arginines** or dipeptides. Although the cDNA sequence predicted eight sites of heterogeneity among the **filaggrin** domains, only one of these was observed. An additional unpredicted site of heterogeneity was also seen. Comparison of the peptides from **filaggrin** with those of **profilaggrin** revealed several peptides unique to **filaggrin**, specifically at the new amino- and carboxyltermini, that result from proteolytic processing of the linker region of **profilaggrin**. Both the amino- and carboxyl-termini were "ragged", suggesting that processing may involve exopeptidase action after an initial endopeptidase cleavage. The average mass of this mixture of **filaggrins** was determined by electrospray mass spectrometry to be 42 452 Da, in reasonable agreement with that predicted from the mass spectrometric analysis of the terminal sequences. The linker peptide of rat **profilaggrin** was found in two forms, which differed only in the phosphorylation state of serine 22.
CC Cytology and Cytochemistry - Animal *02506
Genetics and Cytogenetics - Animal *03506
Biochemical Methods - Proteins, Peptides and Amino Acids 10054
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines *10062
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - Molecular Properties and Macromolecules *10506
Biophysics - Membrane Phenomena *10508
Enzymes - Methods 10804
Enzymes - Chemical and Physical *10806
Metabolism - Proteins, Peptides and Amino Acids *13012
Metabolism - Nucleic Acids, Purines and Pyrimidines *13014
Integumentary System - Physiology and Biochemistry *18504
BC Muridae *86375
IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; Enzymology (Biochemistry and Molecular Biophysics); Genetics; Integumentary System (Chemical Coordination and Homeostasis); Membranes (Cell Biology); Metabolism

IT Chemicals & Biochemicals
PROTEASE
IT Sequence Data
amino acid sequence; molecular sequence data
IT Miscellaneous Descriptors
DEVELOPMENT; HUMAN SKIN
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Muridae (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman vertebrates; nonhuman mammals; rodents; vertebrates
RN 9001-92-7 (PROTEASE)

L100 ANSWER 32 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1993:500362 BIOSIS
DN PREV199396124369
TI The cytokeratin filament-aggregating protein **filaggrin** is the target of the so-called "antikeratin **antibodies**," **autoantibodies** specific for **rheumatoid arthritis**
AU Simon, Michel; Girbal, Elisabeth; Sebbag, Mireille; Gomes-Daudrix, Veronique; Vincent, Christian; Salama, Gilles; Serre, Guy (1)
CS (1) Lab. Biologie Cellulaire, C.H.U. Purpan, Place du Dr. Baylac, 31059 Toulouse Cedex France
SO Journal of Clinical Investigation, (1993) Vol. 92, No. 3, pp. 1387-1393. ISSN: 0021-9738.
DT Article
LA English
AB In **rheumatoid arthritis** (RA), the high diagnostic value of serum **antibodies** to the stratum corneum of rat esophagus epithelium has been widely reported. These so-called "antikeratin **antibodies**," detected by indirect immunofluorescence, were found to be **autoantibodies** since they also labeled human epidermis. Despite their name, the actual target of these **autoantibodies** was not known. In this study, a 40-kD protein (designated as 40K), extracted from human epidermis and specifically immunodetected by 75% of RA sera, was purified and identified as a neutral/acidic isoform of basic **filaggrin**, a cytokeratin filament-aggregating protein, by peptide mapping studies and by the following evidences: (a) mAbs specific for **filaggrin** reacted with the 40K protein; (b) the **autoantibodies**, affinity-purified from RA sera on the 40K protein, immunodetected purified **filaggrin** ; (c) the reactivity of RA sera to the 40K protein was abolished after immunoadsorption with purified **filaggrin**; (d) the 40K protein and **filaggrin** had similar amino acid compositions. Furthermore, **autoantibodies** against the 40K protein and the so-called "antikeratin **antibodies**" were shown, by immunoadsorption experiments, to be largely the same. The identification of **filaggrin** as a RA-specific autoantigen could contribute to the understanding of the pathogenesis of this disease and, ultimately, to the development of methods for preventing the autoimmune response.
CC Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biochemical Studies - Carbohydrates 10068
Pathology, General and Miscellaneous - Inflammation and Inflammatory Disease *12508
Bones, Joints, Fasciae, Connective and Adipose Tissue - Pathology *18006
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508
BC Hominidae *86215
IT Major Concepts
Clinical Immunology (Human Medicine, Medical Sciences); Pathology; Skeletal System (Movement and Support)
IT Miscellaneous Descriptors

MAJOR HISTOCOMPATIBILITY COMPLEX CLASS I PRESENTATION;
UBIQUITIN-DEPENDENT PATHWAY
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae); U937 (Hominidae): cell line
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates

L100 ANSWER 33 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1991:502029 BIOSIS
DN BA92:124989
TI ANTIPERINUCLEAR FACTOR A MARKER **AUTOANTIBODY** FOR **RHEUMATOID ARTHRITIS** COLOCALIZATION OF THE PERINUCLEAR FACTOR AND **PROFILAGGRIN**.
AU HOET R M A; BOERBOOMS A M T; ARENDS M; RUITER D J; VAN VENROOIJ W J
CS DEP. BIOCHEM., UNIV. NIJMEGEN, P.O. BOX 9101, 6500 HB NIJMEGEN, NETHERLANDS.
SO ANN RHEUM DIS, (1991) 50 (9), 611-618.
CODEN: ARDIAO. ISSN: 0003-4967.
FS BA; OLD
LA English
AB The antiperinuclear factor, an **autoantibody** specific for **rheumatoid arthritis**, was found in 51/63 (81%) patients with **rheumatoid arthritis** by indirect immunofluorescence on human buccal mucosa cells. The sensitivity of the antiperinuclear factor test was increased by pretreating the buccal mucosa cells with 0.5% Triton-X100. The specificity of the test for **rheumatoid arthritis** as compared with control serum samples was maintained. The localisation of the perinuclear factor in the keratohyalin granules of the buccal mucosa cells was verified by immunoelectron microscopy. The perinuclear factor was found to be an insoluble protein whose antigenicity was sensitive to various fixation procedures. In serum samples from patients with **rheumatoid arthritis** there was a positive correlation between the presence of antiperinuclear factor and the presence of the so called antikeratin **antibodies** as detected by immunofluorescence on unfixed rat oesophagus cryostat sections. No relation was found between the presence of the perinuclear factor and either the **rheumatoid** factor, Epstein-Barr virus components, or any cytokeratin. By double immunofluorescence an exact colocalisation of the perinuclear factor and **profilaggrin** was found. Although the precise biochemical identity of the perinuclear factor remains unclear, our results suggest that it is a protein only present in the fully differentiated squamous epithelial call layer.
CC Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biochemical Studies - Carbohydrates 10068
Pathology, General and Miscellaneous - Inflammation and Inflammatory Disease *12508
Bones, Joints, Fasciae, Connective and Adipose Tissue - Pathology *18006
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508
BC Hominidae 86215
IT Miscellaneous Descriptors
HUMAN **RHEUMATOID** FACTOR DIAGNOSTIC MARKER

L100 ANSWER 34 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1991:272419 BIOSIS
DN BA92:5034
TI THE PERINUCLEAR FACTOR **RHEUMATOID ARTHRITIS**-SPECIFIC AUTOANTIGEN IS NOT PRESENT IN KERATOHYALIN GRANULES OF CULTURED BUCCAL MUCOSA CELLS.
AU HOET R M; VOORSMIT R A C A; VAN VENROOIJ W J
CS DEP. BIOCHEMISTRY, UNIV. NIJMEGEN, PO BOX 9101, 6500 HB NIJMEGEN, THE NETHERLANDS.

SO CLIN EXP IMMUNOL, (1991) 84 (1), 59-65.
CODEN: CEXIAL. ISSN: 0009-9104.
FS BA; OLD
LA English
AB **Rheumatoid arthritis** patients have **antibodies** in their serum directed against the perinuclear factor, a protein component present in keratohyalin granules in the cytoplasm of human buccal mucosa cells. The anti-perinuclear factor (APF) can only be detected by an indirect immunofluorescence test performed on fresh bucal mucosa cells from 'selected donors'. To obtain a more reliable antigen source and to gain more insight into the origin and nature of the perinuclear factor we attempted to culture perinuclear factor-containing buccal mucosa cells. Here we describe the successful culturing of such cells, which, however, did not contain keratohyalin granules nor the perinuclear factor. By adding the phorbol ester 12-o-tetradecanoylphorbol-13-acetate (TPA) we were able to induce keratohyalin granules in both cultured primary buccal mucosa cells and a squamous carcinoma cell line of the cheek (SqCC/Y1). These induced keratohyalin granules do contain the protein **profilaggrin**, which in vivo, in fresh buccal mucosa cells, co-localizes with the perinuclear factor. However, we were not able to demonstrate the presence of the perinuclear factor, not even after induction of terminal differentiation of the cultured cells nor after Epstein-Barr virus infection. Our results suggest that the perinuclear factor, in contrast to **profilaggrin**, is not an integral component of buccal mucosa cells.
CC Cytology and Cytochemistry - Human *02508
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Pathology, General and Miscellaneous - Inflammation and Inflammatory Disease *12508
Metabolism - Proteins, Peptides and Amino Acids *13012
Bones, Joints, Fasciae, Connective and Adipose Tissue - Pathology *18006
Integumentary System - Physiology and Biochemistry *18504
In Vitro Studies, Cellular and Subcellular 32600
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508
BC Hominidae 86215
IT Miscellaneous Descriptors
HUMAN **FILAGGRIN** KERATINOCYTE ANTIPERINUCLEAR FACTOR

L100 ANSWER 35 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1988:155923 BIOSIS
DN BA85:79576
TI ICHTHYOSIFORM DERMATOSIS AND DEAFNESS REPORT OF A CASE AND REVIEW OF THE LITERATURE.
AU BADEN H P; BRONSTEIN B R
CS DEP. DERMATOL., HARVARD MED. SCH., MASS. GEN. HOSP., BOSTON, MASS., USA.
REPRINTS NOT AVAILABLE.
SO ARCH DERMATOL, (1988) 124 (1), 102-106.
CODEN: ARDEAC. ISSN: 0003-987X.
FS BA; OLD
LA English
AB A patient suffering from an ichthyosiform dermatosis, partial deafness, and pes cavus is described. Most of the body surface was covered by fine white scales; red scaling plaques were present on the arms. There were slight hyperkeratoses of the palms and soles, keratosis pilarislike lesions with perifollicular redness on the trunk, and multifocal alopecia. A biopsy specimen of the scaly erythematous plaque demonstrated hyperkeratosis with follicular plugging, papillomatosis, and acanthosis. Direct immunofluorescence studies of lesional skin using monoclonal **antibodies** to epidermal prekeratin, **filaggrin**, and involucrin revealed normal staining patterns. The patient's cultured keratinocytes were morphologically unremarkable and contained **profilaggrin**, involucrin, and a normal complement of cytokeratins. The expression of the disease may not occur in cultured cells, because they lack many features of fully keratinized cells. A review of the

literature concerning ichthyosis and deafness reveals that the constellation of cutaneous and extracutaneous abnormalities in this case does not exactly conform to that in previously reported cases. Precise classification of the patient's disorder will require demonstration of the basic defect(s).

CC Microscopy Techniques - Histology and Histochemistry 01056
Microscopy Techniques - Electron Microscopy 01058
Cytology and Cytochemistry - Human *02508
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biochemical Studies - Carbohydrates 10068
Anatomy and Histology, General and Comparative - Microscopic and Ultramicroscopic Anatomy *11108
Chordate Body Regions - Extremities 11318
Pathology, General and Miscellaneous - General *12502
Pathology, General and Miscellaneous - Inflammation and Inflammatory Disease *12508
Bones, Joints, Fasciae, Connective and Adipose Tissue - Pathology *18006
Integumentary System - General; Methods 18501
Integumentary System - Pathology *18506
Sense Organs, Associated Structures and Functions - Pathology *20006
Sense Organs, Associated Structures and Functions - Deafness, Speech and Hearing *20008
Immunology and Immunochemistry - General; Methods 34502

BC Hominidae 86215

IT Miscellaneous Descriptors
HUMAN PES CAVUS SCALING PLAQUE HYPERKERATOSIS ALOPECIA PAPILLOMATOSIS ACANTHOSIS ICHTHYOSIS

L100 ANSWER 36 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

AN 1987:210494 BIOSIS

DN BA83:108124

TI ARRESTED EPIDERMAL MORPHOGENESIS IN THREE NEWBORN INFANTS WITH A FATAL GENETIC DISORDER RESTRICTIVE DERMOPATHY.

AU HOLBROOK K A; DALE B A; WITT D R; HAYDEN M D; TORIELLO H V

CS DEP. OF BIOL. STRUCTURE SM-20, UNIV. OF WASH. SCH. OF MED., SEATTLE, WASH. 98195.

SO J INVEST DERMATOL, (1987) 88 (3), 330-339.
CODEN: JIDEAE. ISSN: 0022-202X.

FS BA; OLD

LA English

AB Two sibs and one unrelated infant were born prematurely with taut, shiny, restrictive skin that was abnormal in structure, organization, biochemistry, and state of differentiation. Prominent abnormalities in all regions of the skin were recognized by light and electron microscopy, immunohistochemistry, and biochemistry. The epidermis was hyperplastic, hyperkeratotic, and parakeratotic. Keratohyaline granules were abnormal in structure, but the keratohyalin-derived protein **filaggrin** was apparently normal in quantity and biochemistry. The epidermal cells contained less than the expected quantity of high-molecular-weight, differentiation-specific keratins and the tissue stained with antikeratin **antibodies** in an aberrant pattern. Additional 48 and 56 kDa keratin polypeptides, indicative of a hyperproliferative state, were expressed. The dermal-epidermal junction was remarkably flat and the dermis was thinner than normal. The connective tissue appeared stretched and was oriented like tendon rather than dermis. Collagen fiber bundles and fibrils were smaller in diameter than normal. The nails were normal but other epidermal appendages such as the pilsoebaceous structures and the eccrine sweat glands were underdeveloped, suggesting that morphogenesis of these structures was arrested at an early stage in utero. The subcutaneous fat was at least twice the thickness of the dermis. The skin abnormalities appeared to be the cause of the flexion contractions, characteristic facies, and inability to survive because of restricted respiratory movements. The structural and biochemical abnormalities in the skin of affected infants may serve as markers for prenatal and postnatal diagnosis of the disorder, and may provide insight into the basic

mechanism of the disease.
CC Microscopy Techniques - Cytology and Cytochemistry 01054
Microscopy Techniques - Histology and Histochemistry 01056
Genetics and Cytogenetics - Human *03508
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Anatomy and Histology, General and Comparative - Microscopic and Ultramicroscopic Anatomy *11108
Pathology, General and Miscellaneous - Diagnostic *12504
Pathology, General and Miscellaneous - Necrosis 12510
Metabolism - Proteins, Peptides and Amino Acids *13012
Metabolism - Metabolic Disorders *13020
Bones, Joints, Fasciae, Connective and Adipose Tissue - Pathology *18006
Integumentary System - Pathology *18506
Pediatrics *25000
Developmental Biology - Embryology - Pathological *25503
Developmental Biology - Embryology - Morphogenesis, General *25508
BC Hominidae 86215
IT Miscellaneous Descriptors
HUMAN DIAGNOSIS KERATIN HYPERPROLIFERATION SUBCUTANEOUS FAT CONNECTIVE TISSUE KERATOHYALINE GRANULE

L100 ANSWER 37 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1986:320432 BIOSIS
DN BA82:44737
TI ISOLATION AND CHARACTERIZATION OF A 30-KILODALTON MEMBRANE GLYCOPROTEIN FROM HUMAN STRATUM CORNEUM.
AU CHEN S-J; RAJARAMAN S; MILLER J; KALMAZ G D; BRYSK M M
CS DEP. DERMATOL., UNIV. TEXAS MED. BRANCH, GALVESTON, TEX. 77550, USA.
SO BIOCHIM BIOPHYS ACTA, (1986) 881 (3), 375-382.
CODEN: BBACAQ. ISSN: 0006-3002.
FS BA; OLD
LA English
AB Using iodinated concanavalin A in conjunction with gel electrophoresis, we have identified a 30 kDa glycoprotein in the stratum corneum of human skin. We isolated this glycoprotein by extraction in nonionic detergent, affinity chromatography and preparative gel electrophoresis. It binds to concanavalin A but not to three other lectins. The purified glycoprotein migrates at 30 kDa whether or not reducing agents are present. It is rich in histidine and lysine, but lacks **arginine**, proline, tyrosine and methionine. It is clearly distinct from **filaggrin**. We prepared a monospecific polyclonal antibody to this glycoprotein and localized it by immunohistochemistry exclusively to the cell membrane of corneocytes. We postulate that the glycoprotein may play a role in the cohesion and desquamation of corneocytes.
CC Cytology and Cytochemistry - Human *02508
Biochemical Methods - Proteins, Peptides and Amino Acids 10054
Biochemical Methods - Carbohydrates 10058
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biochemical Studies - Carbohydrates *10068
Biophysics - Molecular Properties and Macromolecules *10506
Biophysics - Membrane Phenomena *10508
Integumentary System - Physiology and Biochemistry *18504
BC Hominidae 86215
IT Miscellaneous Descriptors
CORNEOCYTE HISTIDINE LYSINE
RN 56-87-1Q, 6899-06-5Q (LYSINE)
71-00-1Q, 7006-35-1Q (HISTIDINE)

L100 ANSWER 38 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1985:271170 BIOSIS
DN BA79:51166
TI **FILAGGRIN** DISTRIBUTION IN KERATOACANTHOMAS AND SQUAMOUS CELL CARCINOMA.
AU KLEIN-SZANTO A J P; BARR R J; REINERS J J JR; MAMRACK M D
CS UNIVERSITY TEXAS SYSTEM CANCER CENTER, SCIENCE PARK-RESEARCH DIVISION, PO

BOX 389, SMITHVILLE, TEX. 78957.
SO ARCH PATHOL LAB MED, (1984) 108 (11), 888-890.
CODEN: APLMAS. ISSN: 0096-8528.
FS BA; OLD
LA English
AB The cellular distribution of **filaggrin**, a histidine-rich protein present in the granular and horny layers of normal epidermis, was investigated in 27 human keratoacanthomas and squamous cell carcinomas of the skin using an indirect immunohistochemical procedure with rabbit antimouse **filaggrin** Ig. Using the same working dilution of the primary **antibody**, normal epidermis, as well as all keratoacanthomas, exhibited a positive immunoperoxidase or immunofluorescence stain in the granular and horny layers. All squamous cell carcinomas, except 1, were negative. With higher concentrations of primary **antibody**, 2 additional carcinomas showed a weak, positive staining. The absence of **filaggrin** in squamous carcinomas could be of use in the differential diagnosis of cutaneous tumors.
CC Cytology and Cytochemistry - Human *02508
Clinical Biochemistry; General Methods and Applications *10006
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines 10062
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Pathology, General and Miscellaneous - Diagnostic 12504
Bones, Joints, Fasciae, Connective and Adipose Tissue - Pathology *18006
Neoplasms and Neoplastic Agents - Diagnostic Methods *24001
Neoplasms and Neoplastic Agents - Biochemistry *24006
Immunology and Immunochemistry - General; Methods 34502
BC Hominidae 86215
IT Miscellaneous Descriptors
HUMAN CUTANEOUS TUMOR HISTIDINE-RICH PROTEIN IMMUNOHISTOCHEMICAL PROCEDURE PRIMARY **ANTIBODY** DIFFERENTIAL DIAGNOSIS
RN 71-00-1Q, 7006-35-1Q (HISTIDINE)

L100 ANSWER 39 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1984:299438 BIOSIS
DN BA78:35918
TI HIGH MOLECULAR WEIGHT PRECURSOR OF EPIDERMAL **FILAGGRIN** AND HYPOTHESIS FOR ITS TANDEM REPEATING STRUCTURE.
AU LONSDALE-ECCLES J D; RESING K A; MEEK R L; DALE B A
CS DEPARTMENT OF PERIODONTICS, UNIVERSITY OF WASHINGTON, SEATTLE, WASH. 98195.
SO BIOCHEMISTRY, (1984) 23 (6), 1239-1245.
CODEN: BICHAW. ISSN: 0006-2960.
FS BA; OLD
LA English
AB **Filaggrin** is a histidine-rich protein that is intimately involved in mammalian epidermal keratinization. Using a combination of immunologic and in vivo pulse-chase studies with radiolabeled histidine and phosphate, the phosphorylated precursor of both rat and mouse **filaggrin** has an apparent MW much higher than previously realized (6 .times. 105 and 3.9 .times. 105, respectively). These high-MW **filaggrin** precursors can be rapidly labeled with histidine and extracted from the epidermis under denaturing conditions. More than half of the label incorporated in the precursor at 2 h is found in **filaggrin** at 24 h after injection, even though **filaggrin** is < 10% of the size of the precursor. Limited proteolytic digestion of the precursor in vitro results in the formation of an oligomeric series of peptides based on a phosphorylated fragment slightly larger than **filaggrin** itself. More extensive digestion of this fragment shows that it is composed of **filaggrin** with few or no additional unrelated peptides, suggesting that the major part of the high MW **filaggrin** precursor must be composed of repeated domains of **filaggrin**. Because the primary translation product of **filaggrin** mRNA is large, these domains are repeated in tandem. From MW computations and peptide map analyses, the **filaggrins**

are themselves composed of multiple repeating units of an unidentified peptide of approximately MW 8600. This value is derived from the MW of **filaggrin** from several mammalian species that differ by integral multiples of 8600. A model for the structure of the high MW precursor of **filaggrin** is presented. It has 2 types of repeating units: those that make up the **filaggrin** molecule itself and the tandem repeated copies of **filaggrin**.

CC Microscopy Techniques - Histology and Histochemistry 01056
Mathematical Biology and Statistical Methods 04500
Radiation - Radiation and Isotope Techniques 06504
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines 10062
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biochemical Studies - Minerals 10069
Biophysics - General Biophysical Techniques 10504
Biophysics - Molecular Properties and Macromolecules *10506
Biophysics - Bioenergetics: Electron Transport and Oxidative Phosphorylation *10510
Biophysics - Biocybernetics 10515
Metabolism - Energy and Respiratory Metabolism *13003
Metabolism - Proteins, Peptides and Amino Acids *13012
Bones, Joints, Fasciae, Connective and Adipose Tissue - General; Methods *18001
Integumentary System - General; Methods *18501
Integumentary System - Physiology and Biochemistry *18504
Immunology and Immunochemistry - General; Methods 34502

BC Muridae 86375

IT Miscellaneous Descriptors
RAT MOUSE RADIO LABELED HISTIDINE PHOSPHATE TRACER MESSENGER RNA IMMUNO HISTOCHEMISTRY PHOSPHORYLATION KERATINIZATION MOLECULAR MODEL

RN 14265-44-2 (PHOSPHATE)
71-00-1Q, 7006-35-1Q (HISTIDINE)

L100 ANSWER 40 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1984:283367 BIOSIS
DN BA78:19847
TI HISTIDINE-RICH PROTEINS **FILAGGRINS** STRUCTURAL AND FUNCTIONAL HETEROGENEITY DURING EPIDERMAL DIFFERENTIATION.
AU HARDING C R; SCOTT I R
CS ENVIRONMENTAL SAFETY LABORATORY, COLWORTH HOUSE, SHARNBROOK BEDFORD MK44 1LQ, ENGLAND.
SO J MOL BIOL, (1983) 170 (3), 651-674.
CODEN: JMOBAK. ISSN: 0022-2836.
FS BA; OLD
LA English
AB The urea-soluble protein profiles of guinea pig, rat, mouse and human epidermis were compared by non-equilibrium pH gradient/sodium dodecyl sulfate two-dimensional gel electrophoresis. The histidine-rich proteins (**filaggrins**) were identified firstly by their characteristic specificity and kinetics of labeling with [3H]histidine and [32P]phosphate, and secondly by their ability in vitro to aggregate keratin filaments specifically into bundles. In all species the phosphorylated **filaggrin** precursor, **profilaggrin**, is resolved as a single or doublet band with an apparent MW > 30,000 and a neutral or slightly acidic iso-electric point. The strongly basic **filaggrins** produced from similar **profilaggrins** form MW families that are clearly species specific. In rat and man there is a single, principal MW form of **filaggrin** (45,000 and 38,000, respectively), while mouse and guinea pig have heterogeneous families, including high MW variants (> 200,000). Even **filaggrins** of a particular molecular weight are not homogeneous proteins, but consist of a number of iso-electric variants, some of which are considerably less basic than the bulk of the **filaggrins**. Incorporation studies using [3H]**arginine** and [32P]phosphate indicate that the iso-electric variance is not due to residual phosphate, following **profilaggrin** breakdown, but rather to a conversion of basic **arginine** residues into neutral **citrulline** residues. **Filaggrins** of all

the MW from all the species studied share the ability to aggregate keratin filaments into large, insoluble macrofibrils. The more acidic iso-electric variants have lower affinities for keratin, particularly in man and guinea pig where the most acidic **filaggrins** have completely lost the ability to aggregate keratins. The possibility that a loss of keratin binding ability, resulting in a loosening of the keratin fiber/ **filaggrin** matrix is necessary before the normal complete proteolysis of the **filaggrins** can occur is discussed.

CC Microscopy Techniques - Histology and Histochemistry 01056
Cytology and Cytochemistry - Animal *02506
Cytology and Cytochemistry - Human *02508
Radiation - Radiation and Isotope Techniques 06504
Biochemical Methods - Proteins, Peptides and Amino Acids 10054
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biochemical Studies - Minerals 10069
Biophysics - General Biophysical Techniques 10504
Biophysics - Molecular Properties and Macromolecules *10506
Biophysics - Membrane Phenomena *10508
Physiology, General and Miscellaneous - Comparative *12003
Movement 12100
Metabolism - Proteins, Peptides and Amino Acids *13012
Bones, Joints, Fasciae, Connective and Adipose Tissue - Physiology and Biochemistry *18004
Integumentary System - General; Methods *18501
Integumentary System - Physiology and Biochemistry *18504

BC Hominidae 86215
Caviidae 86300
Muridae 86375

IT Miscellaneous Descriptors
RAT MOUSE GUINEA-PIG HUMAN TRITIUM LABELED HISTIDINE **ARGININE**
PHOSPHORUS-32 LABELED PHOSPHATE TRACER KERATIN **PROFILAGGRIN**
UREA ELECTROPHORESIS PROTEOLYSIS

RN 57-13-6 (UREA)
10028-17-8 (TRITIUM)
14265-44-2 (PHOSPHATE)
14596-37-3 (PHOSPHORUS-32)
71-00-1Q, 7006-35-1Q (HISTIDINE)
74-79-3Q, 7004-12-8Q (ARGININE)

L100 ANSWER 41 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1984:87128 BIOSIS
DN BR27:3620
TI BIOSYNTHESIS OF MOUSE EPIDERMAL **FILAGGRIN**.
AU STEINERT P M; HINTNER H K
CS DERMATOLOGY BRANCH, NATL. CANCER INST., NIH, BETHESDA, MD.
SO 23RD ANNUAL MEETING OF THE AMERICAN SOCIETY FOR CELL BIOLOGY, SAN ANTONIO, TEX., USA, NOV. 29-DEC. 3, 1983. J CELL BIOL. (1983) 97 (5 PART 2), 224A. CODEN: JCLBA3. ISSN: 0021-9525.
DT Conference
FS BR; OLD
LA English
CC General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520
Cytology and Cytochemistry - Animal *02506
Radiation - Radiation and Isotope Techniques 06504
Biochemical Methods - Proteins, Peptides and Amino Acids 10054
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - General Biophysical Techniques 10504
Movement 12100
Metabolism - General Metabolism; Metabolic Pathways *13002
Metabolism - Proteins, Peptides and Amino Acids *13012
Integumentary System - General; Methods *18501
Integumentary System - Physiology and Biochemistry *18504
Developmental Biology - Embryology - Morphogenesis, General *25508
Tissue Culture, Apparatus, Methods and Media *32500
In Vitro Studies, Cellular and Subcellular 32600

BC Muridae 86375
IT Miscellaneous Descriptors
ABSTRACT PHOSPHORUS-32 LABELED ORTHO PHOSPHATE TRITIUM LABELED HISTIDINE **ARGININE** TRACER UROCANIC-ACID KERATIN SERINE COLUMN CHROMATOGRAPHY CELL CULTURE
RN 104-98-3 (UROCANIC-ACID)
10028-17-8 (TRITIUM)
14265-44-2 (ORTHO PHOSPHATE)
14596-37-3 (PHOSPHORUS-32)
56-45-1Q, 6898-95-9Q (SERINE)
71-00-1Q, 7006-35-1Q (HISTIDINE)
74-79-3Q, 7004-12-8Q (ARGININE)

L100 ANSWER 42 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1983:292289 BIOSIS
DN BA76:49781
TI THE CHARACTERIZATION OF HUMAN EPIDERMAL **FILAGGRIN** A HISTIDINE-RICH KERATIN FILAMENT AGGREGATING PROTEIN.
AU LYNLEY A M; DALE B A
CS DEP. MED., UNIV. WASHINGTON, SEATTLE, WASH. 98195.
SO BIOCHIM BIOPHYS ACTA, (1983) 744 (1), 28-35.
CODEN: BBACAQ. ISSN: 0006-3002.
FS BA; OLD
LA English
AB **Filaggrin**.is a histidine-rich, cationic protein that aggregates with keratin filaments in vitro and may function as the keratin matrix protein in the terminally differentiated cells of the epidermis. This protein has been previously isolated from rodent epidermis. A similar protein from human skin is identified, isolated and characterized by biochemical and immunologic techniques. Indirect immunofluorescence of human skin using antiserum to rat **filaggrin** gave positive immunofluorescence of keratohyalin granules and the stratum corneum. This indicated the presence of a human **filaggrin** in the epidermis in a localization similar to that of the rodent. The protein isolated from human epidermis and purified by ion-exchange chromatography and preparative gel electrophoresis crossreacts with antibody to rat **filaggrin** and migrates as a doublet of MW .apprx. 35,000 on SDS[sodium dodecyl sulfate]-polyacrylamide gels. It is relatively rich in polar amino acids such as histidine, **arginine**, serine and glycine, but is poor in nonpolar amino acids. Unlike rodent **filaggrin**, the human protein contains ornithine. This protein aggregates with human keratin filaments, forming compact macrofibrils in a manner analogous to that of rodent **filaggrin**. The human epidermal protein has many of the characteristics of rodent **filaggrin** and may function as the human keratin matrix protein.
CC Cytology and Cytochemistry - Animal 02506
Cytology and Cytochemistry - Human *02508
Comparative Biochemistry, General *10010
Biochemical Methods - Proteins, Peptides and Amino Acids 10054
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - General Biophysical Techniques 10504
Biophysics - Molecular Properties and Macromolecules *10506
Biophysics - Membrane Phenomena *10508
Physiology, General and Miscellaneous - Comparative *12003
Movement 12100
Integumentary System - Physiology and Biochemistry *18504
Chordata, General and Systematic Zoology - Mammalia *62520
BC Hominidae 86215
Rodentia - Unspecified 86265
Muridae 86375
IT Miscellaneous Descriptors
RODENT RAT AMINO-ACIDS MOLECULAR WEIGHT MACRO FIBRILS MATRIX PROTEIN
RN 71-00-1Q, 7006-35-1Q (HISTIDINE)

=> fil wpix

FILE 'WPIX' ENTERED AT 10:17:02 ON 14 MAR 2002

FILE LAST UPDATED: 13 MAR 2002 <20020313/UP>
MOST RECENT DERWENT UPDATE 200217 <200217/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> SDI'S MAY BE RUN ON EVERY UPDATE OR MONTHLY AS OF JUNE 2001.
(EVERY UPDATE IS THE DEFAULT). FOR PRICING INFORMATION
SEE HELP COST <<<

>>> FOR UP-TO-DATE INFORMATION ABOUT THE DERWENT CHEMISTRY
RESOURCE, PLEASE VISIT
http://www.derwent.com/chemistryresource/index.html <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES,
SEE http://www.derwent.com/dwpi/updates/dwpicov/index.html <<<

=> d all abeq tech tot l115

L115 ANSWER 1 OF 6 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD
AN **2001-114394** [13] WPIX
DNN **N2001-084087** DNC **C2001-034134**
TI New **citrulline**-containing polypeptide from fibrin, useful for diagnosis and treatment of **rheumatoid polyarthritis**.
DC B04 D16 S03
IN **SEBBAG, M; SERRE, G**
PA (UYTO-N) UNIV TOULOUSE SABATIER PAUL
CYC 21
PI FR 2795735 A1 20010105 (200113)* 23p C07K014-745
WO 2001002437 A1 20010111 (200113) FR C07K014-75
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: CA JP US
ADT FR 2795735 A1 FR 1999-8470 19990701; WO 2001002437 A1 WO 2000-FR1857 20000630
PRAI FR 1999-8470 19990701
IC ICM C07K014-745; C07K014-75
ICS A61K038-36; A61P019-02; A61P029-00; A61P037-00; G01N033-53; G01N033-68
AB FR 2795735 A UPAB: 20010307
NOVELTY - **Citrulline** (**Cit**) containing polypeptide (I) derived from all or part of the alpha - or beta -chains of fibrin (from a vertebrate) by substitution of at least one **arginine** residue by **Cit**, is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) antigenic composition for detecting **autoantibodies** (AAb) specific for **rheumatoid polyarthritis** (RP), comprising at least one (I), optionally labeled and/or conjugated to a carrier protein;
(2) method for detecting AAb;
(3) kit for detecting AAb; and
(4) pharmaceutical composition containing at least one (I) as active ingredient.
ACTIVITY - Anti-**arthritic**; anti-inflammatory.
No biological data is given.
MECHANISM OF ACTION - Neutralization of an autoimmune response, especially inhibition of fixation of humoral/cellular effectors of the response. The antigen responsible for the autoimmune response in **rheumatoid polyarthritis** has been identified as **citrulline**-containing derivatives of fibrin chains.
USE - (I) are used for in vitro diagnosis of **rheumatoid polyarthritis** (RP), by detecting disease-specific **autoantibodies**, and therapeutically for neutralizing the RP-associated autoimmune response.

ADVANTAGE - (I) can detect **autoantibodies** associated with **rheumatoid polyarthritis** in serum with high sensitivity.
Dwg.0/3
FS CPI EPI
FA AB; DCN
MC CPI: B04-G01; B04-N0200E; B11-C07A; B12-K04; B14-C06; B14-C09B; D05-H07; D05-H09; D05-H11
EPI: S03-E14H
TECH UPTX: 20010307
TECHNOLOGY FOCUS - BIOLOGY - Preferred Polypeptide: (I) contains at least 5, particularly at least 10, consecutive amino acids from the fibrin chains, especially from a mammalian, specifically human, fibrin.
Preferred Method: To detect AAb, a test sample is incubated with (I) and any AAb-antigen complexes formed are detected conventionally.
Preferred Kits: The kits contain at least one (I) plus standard buffers and reagents for forming and detecting an immune complex.
Preparation: (I) may be obtained from fibrin or fibrinogen (natural, recombinant or synthetic), or **arginine**-containing fragments, by treatment with peptidyl **arginine** deiminase.
Preferred Process: Proteins were extracted from synovial tissues, separated by electrophoresis and tested for reaction with anti-**filiggrin** auto-**antibodies** (AAF). Two proteins (64-78 and 55-61 kDa) were recognized in urea/dithiothreitol extracts from patients with RP. Partial sequencing of these proteins show them to be encoded by the genes for the alpha and beta-fibrin chain precursors. Further analysis showed that AAF are not significantly reactive with the normal fibrinogen chains but react strongly with those chains that have been deiminated in vivo to convert **arginine** to **Cit**.

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I) may be produced by usual methods of peptide synthesis, with direct incorporation of **Cit** during synthesis. Synthetic (I) may be pseudopeptides with retro or retro-inverso residues (to increase resistance to proteases).

L115 ANSWER 2 OF 6 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD
AN **1999-407453** [35] WPIX
DNN **N1999-303959** DNC **C1999-120603**
TI Peptide containing epitope recognized by anti-**filaggrin antibodies**, used as immunoassay reagents for diagnosis of **rheumatoid polyarthritis**.
DC B04 S03
IN **ARNAUD, M; DALBON, P; GIRBAL, N E; JOLIVET, M; JOLIVET, R C; SEBBAG, M; SERRE, G B R; SIMON, M; VINCENT, C; GIRBAL-NEUHAUSER, E; JOLIVET-REYNAUD, C; SERRE, G**
PA (INMR) **BIO MERIEUX**; (INMR) **BIOMERIEUX SA**
CYC 77
PI FR 2773157 A1 19990702 (199935)* 21p C07K014-47
WO 9935167 A1 19990715 (199935) FR C07K014-47
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AU BA BB BG BR CA CN CU CZ EE GD GE HR HU ID IL IN IS JP KG KP KR LC LK LR LT LV MG MK MN MX NO NZ PL RO SG SI SK SL TR TT UA US UZ VN YU ZW
AU 9919717 A 19990726 (199952) C07K014-47
EP 1042366 A1 20001011 (200052) FR C07K014-47
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
ADT FR 2773157 A1 FR 1997-16673 19971230; WO 9935167 A1 WO 1998-FR2899 19981229; AU 9919717 A AU 1999-19717 19981229; EP 1042366 A1 EP 1998-964536 19981229, WO 1998-FR2899 19981229
FDT AU 9919717 A Based on WO 9935167; EP 1042366 A1 Based on WO 9935167
PRAI FR 1997-16673 19971230
IC ICM C07K014-47
ICS A61K038-17; G01N033-53; G01N033-564
AB FR 2773157 A UPAB: 19990902

NOVELTY - Peptide (I) contains an epitope, recognized by anti-**filaggrin antibodies** (Ab) present in the serum of patients with **rheumatoid polyarthritis** (RP), comprises a tripeptide motif centered on a **citrulline** (**Cit**) residue present in at least one of three peptides of 49, 14 and 14 amino acids (sequences reproduced; fragments of **filaggrin**).

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) artificial antigen (AAg), recognized specifically by Ab, containing, or consisting of, at least one (I);

(2) antigenic composition for diagnosis of RP containing at least one (I) or AAg, optionally labeled or conjugated to a carrier molecule; and

(3) kits for detecting Ab containing (I) or AAg, plus suitable buffers and reagents.

ACTIVITY - None given.

MECHANISM OF ACTION - None given.

USE - (I) are used as antigen for in vitro detection of Ab, for diagnosis of RP, in standard immunoassays.

ADVANTAGE - Ab are markers of RP and their detection makes possible diagnosis at an early stage.

Dwg.0/0

FS CPI EPI

FA AB; DCN

MC CPI: B11-C07A; B12-K04A

EPI: S03-E14H4

TECH UPTX: 19990902

TECHNOLOGY FOCUS - INSTRUMENTATION AND TESTING - Preferred materials: (I) contain the motif Ser-**Cit**-His, particularly derived from the structure (Asp)n-X1-Ser-**Arg**-His-X2-(X3)n

n = 0 or 1;

X1 = Ser or Gly;

X2 = Ser or Pro;

X3 = Gly or **Arg**

. In (I), all amino acids are independently L or D forms, and one or more CONH bonds may be replaced by NHCO.

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I) are produced: (1) by the action of **peptidylarginine** deiminase on **Arg**-containing substrates, which may be natural, recombinant or synthetic, or (2) directly by usual methods of peptide synthesis.

L115 ANSWER 3 OF 6 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD

AN **1999-407426** [35] WPIX

DNC **C1999-120600**

TI **Filaggrin**-derived **citrulline** peptide antigens, useful for treatment of **rheumatoid arthritis**.

DC B04

IN **ARNAUD, M; DALBON, P; GIRBAL, N E; JOLIVET, M; JOLIVET, R C; SEBBAG, M; SERRE, G B R; SIMON, M; VINCENT, C; GIRBAL-NEUHAUSER, E; JOLIVET-REYNAUD, C; SERRE, G**

PA (UYTO-N) UNIV TOULOUSE SABATIER PAUL

CYC 77

PI FR 2773078 A1 19990702 (199935)* 26p A61K038-17

WO 9934819 A2 19990715 (199935) EN 26p A61K038-17

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW

W: AL AU BA BB BG BR CA CN CU CZ EE GD GE HR HU ID IL IN IS JP KG KP KR LC LK LR LT LV MG MK MN MX NO NZ PL RO SG SI SK SL TR TT UA US UZ VN YU ZW

AU 9919718 A 19990726 (199952) A61K038-17

EP 1041997 A2 20001011 (200052) FR A61K038-17

R: AT BE CH DE DK ES FI FR GB IE IT LI NL SE

JP 2002500195 W 20020108 (200206) 27p A61K038-00

ADT FR 2773078 A1 FR 1997-16672 19971230; WO 9934819 A2 WO 1998-FR2900

bad date

19981229; AU 9919718 A AU 1999-19718 19981229; EP 1041997 A2 EP 1998-964537 19981229, WO 1998-FR2900 19981229; JP 2002500195 W WO 1998-FR2900 19981229, JP 2000-527267 19981229

FDT AU 9919718 A Based on WO 9934819; EP 1041997 A2 Based on WO 9934819; JP 2002500195 W Based on WO 9934819

PRAI FR 1997-16672 19971230

IC ICM A61K038-00; A61K038-17
ICS C12N015-09

ICA C07K014-47; C07K016-18

ICI C07K014:47

AB FR 2773078 A UPAB: 19990902
NOVELTY - **Filaggrin**-derived **citrulline** peptide antigens are new.

DETAILED DESCRIPTION - An antigenic peptide, specifically recognized by anti-**filaggrin autoantibodies** present in the serum of patients suffering from **rheumatoid arthritis**, constitutes a peptide derived from all or part of the sequence of a **filaggrin** unit. At least one **arginine** residue is substituted for **citrulline**. The peptide is used to obtain medicines to inhibit the **autoantibodies** from binding their antigenic target.

An INDEPENDENT CLAIM is also included for a pharmaceutical composition for the treatment of **rheumatoid arthritis** characterized in that it contains as main agent at least one antigenic peptide as above.

ACTIVITY - Anti-**arthritic**.

MECHANISM OF ACTION - Anti-**Filiggrin AutoAntibody** Inhibitor.

USE - The antigenic peptide is used to obtain medicines to inhibit anti-**filiggrin autoantibodies** from binding their antigenic target. Pharmaceutical compositions containing the **citrulline** peptides are used for the treatment of **rheumatoid arthritis**. All claimed.

ADVANTAGE - For in vivo administration and use of the antigenic peptides, the amino acids can be changed to the L-forms (especially to increase protease resistance) as well as undergo other modifications to enhance their life in cells.

Dwg.0/3

FS CPI

FA AB; DCN

MC CPI: B04-N02; B11-C07A; B12-K04A

TECH UPTX: 19990902
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Peptide: The antigenic peptide comprises all or part of a sequence derived from amino acids 144-324, 76-144 or 71-119 of a human **filaggrin** unit, where at least one **arginine** residue is substituted for a **citrulline** residue. In particular the antigen comprises all or part of at least one sequence chosen from the following (at least one **arginine** is substituted by a **citrulline**): STGHSGSQHS HTTTQGRSDA SRGSSGSRST SRETRDQEQS GDGSRHSGS; EQSADSSRHS GSGH; or ESSRDGSRHP RSHD. The antigenic peptides contain the tripeptide motif Ser-**Cit**-His, where **Cit** represents **citrulline**.

L115 ANSWER 4 OF 6 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD

AN **1999-385357** [32] WPIX

DNN **N1999-288616** DNC **C1999-113336**

TI New peptide derived from intermediate filament proteins.

DC B04 D16 S03

IN MEHEUS, L; RAYMACKERS, J; UNION, A

PA (INNO-N) INNOGENETICS NV

CYC 84

PI WO 9928344 A2 19990610 (199932)* EN 73p C07K014-47
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD

MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW

AU 9921558 A 19990616 (199945) C07K014-47

EP 949270 A1 19991013 (199947) EN C07K014-47

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI

EP 1034186 A2 20000913 (200046) EN C07K014-47

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI

HU 2000004338 A2 20010228 (200121) C07K014-47

ADT WO 9928344 A2 WO 1998-EP7714 19981130; AU 9921558 A AU 1999-21558 19981130; EP 949270 A1 EP 1998-870078 19980409; EP 1034186 A2 EP 1998-965715 19981130, WO 1998-EP7714 19981130; HU 2000004338 A2 WO 1998-EP7714 19981130, HU 2000-4338 19981130

FDT AU 9921558 A Based on WO 9928344; EP 1034186 A2 Based on WO 9928344; HU 2000004338 A2 Based on WO 9928344

PRAI EP 1998-870078 19980409; EP 1997-870195 19971128

IC ICM C07K014-47

ICS A61K038-17; C07K001-107; C07K016-18; G01N033-564

AB WO 9928344 A UPAB: 19991122

NOVELTY - (A) A novel peptide comprises a sequence of less than 50 amino acids of any variant of natural **filaggrin** or any variant of intermediate filament proteins is new.

DETAILED DESCRIPTION - (A) A novel peptide comprises a sequence of less than 50 amino acids of any variant of natural **filaggrin** or any variant of intermediate filament proteins, comprising at least one **citrulline** residue, and where the presence of the **citrulline** is crucial for reacting with **antibodies** that are present in sera from patients with **rheumatoid arthritis** (RA).

INDEPENDENT CLAIMS are also included for the following:

(1) an **antibody** specifically reactive with the **citrulline** residues of a peptide form as in (A) or specifically reactive with the **citrulline** residues of intermediate filament proteins, and with the **antibody** being preferably a monoclonal **antibody** (MAb);

(2) anti-idiotype **antibody** raised upon immunization with an **antibody** as in (1), with the anti-idiotype **antibody** being specifically reactive with an **antibody** as in (1), to mimic the peptide that contains **citrulline** as in (A), and with the **antibody** being preferably an MAb;

(3) an immunotoxin molecule comprising and/or consisting of cell recognition molecule being a peptide as in (A), or an **antibody** as in (1), to mimic the peptide that contains **citrulline** as in (A), and with the **antibody** being preferably a MAb;

(4) use of intermediate filament protein, preferably vimentin or cytokeratin 1 or cytokeratin 9, or **antibodies** raised upon immunization with intermediate filament proteins or a composition for the preparation of a therapeutic or of a diagnostic for RA;

(5) a diagnostic kit for use in detecting auto-immune diseases such as RA, systemic lupus erythematosus, discoid lupus erythematosus, scleroderma, dermatomyositis and Sjogren's syndrome, the kit comprising at least one peptide as in (A), or an **antibody** as in (1), or an intermediate filament protein, with the peptide, **antibody** or protein being optionally bound to a solid filament.

USE - The peptides constitute immunogenic determinants of **antibodies** present in patients with RA. The peptides, **antibodies**, immunotoxins and intermediate filament proteins can be used for the preparation of a therapeutic or of a diagnostic for RA (claimed). The peptides can also be used for identifying compounds which modulate the interaction between an autoantigen and a RA specific **autoantibody**. The products can also be used for the diagnosis and treatment of other autoimmune diseases e.g. systemic lupus erythematosus, discoid lupus erythematosus, scleroderma, dermatomyositis, or Sjogrens syndrome.

Dwg.0/7

FS CPI EPI
FA AB; DCN
MC CPI: B04-C01; B04-G01; B04-G21; B04-N02; B04-N0200E; B04-N02A; B04-N02A0E; B11-C07A; B12-K04A; B14-C09B; B14-N17; D05-H09; D05-H11; D05-H12A; D05-H17A6; D05-H17B6
EPI: S03-E14H4
TECH UPTX: 19990813
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: The peptides may be produced by classical chemical synthesis, and where **arginine** residues are subsequently derivatized towards **citrulline** residues by contacting the peptide with a **peptidylarginine** deiminase.

TECHNOLOGY FOCUS - BIOLOGY - Preparation: The peptides can also be produced by recombinant DNA techniques.

L115 ANSWER 5 OF 6 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD
AN **1998-207042** [18] WPIX
DNN **N1998-164439** DNC **C1998-065259**
TI Artificial antigen recognised by anti-**filaggrin** auto-**antibodies** - is modified form of **filaggrin** with **citrulline** replacing at least one **arginine**, used for diagnosis of **rheumatoid polyarthritis**.
DC B04 D16 S03
IN **ARNAUD, M; DALBON, P; GIRBAL NEUHAUSER, E; JOLIVET, M; JOLIVET, R C; SEBBAG, M; SERRE, G; SIMON, M; VINCENT, C; GIRBAL-NEUHAUSER, E; JOLIVET-REYNAUD, C**
PA (INMR) **BIOMERIEUX SA**
CYC 20
PI WO 9808946 A1 19980305 (199818)* FR 36p C12N015-12
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: CA US
FR 2752842 A1 19980306 (199818) C07K014-78
EP 929669 A1 19990721 (199933) FR C12N015-12
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE
ADT WO 9808946 A1 WO 1997-FR1541 19970901; FR 2752842 A1 FR 1996-10651 19960830; EP 929669 A1 EP 1997-938965 19970901, WO 1997-FR1541 19970901
FDT EP 929669 A1 Based on WO 9808946
PRAI FR 1996-10651 19960830
IC ICM C07K014-78; C12N015-12
ICS C07K014-47; C12N001-21; C12N009-78; G01N033-53; G01N033-532; G01N033-564; G01N033-68
AB WO 9808946 A UPAB: 19980507
Artificial antigen (Ag) recognised specifically by anti-**filaggrin autoantibodies** (Ab) present in the serum of patients with **rheumatoid polyarthritis** (RPA) is a recombinant or synthetic polypeptide containing at least part of a sequence derived from a **filaggrin** unit, or related molecule, by substitution of at least 1 **arginine** residue by **citrulline** (**Cit**).
USE - Ag are used for in vitro diagnosis of RPA from complex formation with Ab in usual immunoassays.
ADVANTAGE - Replacement of **Arg** by **Cit** is essential for antigen-specific recognition by Ab.
Dwg.0/5
FS CPI EPI
FA AB
MC CPI: B04-B04C2; B04-N02; B12-K04A; D05-H09; D05-H12B2; D05-H17A5
EPI: S03-E14H4

L115 ANSWER 6 OF 6 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD
AN **1992-359287** [44] WPIX
DNN **N1992-273856** DNC **C1992-159509**
TI Antigens recognising **rheumatoid polyarthritis** auto-**antibodies** - useful for in vitro diagnosis, is extracted from

human epidermis or fat oesophageal epithelium.

DC B04 D16 J04 S03

IN **SERRE, G**; SOMME, G; **VINCENT, C**

PA (CLON-N) CLONATEC SA; (CLON-N) CLONATEC; (INMR) **BIOMERIEUX SA**

CYC 19

PI EP 511116 A1 19921028 (199244)* FR 38p C07K015-06
R: AT BE CH DE DK ES FR GB GR IT LI LU MC NL PT SE
WO 9219649 A1 19921112 (199248) 70p C07K015-06
W: CA JP US
FR 2675805 A1 19921030 (199252) 64p C07K015-06
FR 2681600 A1 19930326 (199325) 62p C07K015-06
ES 2036983 T1 19930616 (199327) C07K015-06
JP 06502187 W 19940310 (199415) 17p C07K015-06
US 5888833 A 19990330 (199920) C07K001-00

ADT EP 511116 A1 EP 1992-401185 19920424; WO 9219649 A1 WO 1992-FR371 19920424; FR 2675805 A1 FR 1991-4983 19910426; FR 2681600 A1 FR 1991-11727 19910924; ES 2036983 T1 EP 1992-401185 19920424; JP 06502187 W JP 1992-510455 19920424, WO 1992-FR371 19920424; US 5888833 A Cont of US 1993-958353 19930127, US 1994-253762 19940603

FDT ES 2036983 T1 Based on EP 511116; JP 06502187 W Based on WO 9219649

PRAI FR 1991-4983 19910426; FR 1991-11727 19910924

REP 3.Jnl.Ref; DE 3721790; EP 175310; WO 8907764; 7.Jnl.Ref

IC ICM C07K001-00; C07K015-06
ICS A61K039-00; A61K039-395; C07K003-12; C07K003-20; C07K014-00; C07K015-28; C12P021-08; G01N033-53; G01N033-561; G01N033-564; G01N033-577

AB EP 511116 A UPAB: 19931116
Prepn. contains an antigen with the following properties: (1) can be extracted from human epidermis or rat oesophageal epithelium; (2) is a water-soluble protein; (3) its immunoreactivity is not affected by treatment with nuclease, EtOH or trichloroacetic acid and (4) is specifically recognised by **autoantibodies** (AAb) present in patients with **rheumatoid polyarthritis** (PR).

Also new are individual antigenic components of (A), or of human (pro) **filaggrin**, able to recognise AAb.

(A) from human epidermis is pref. sepd. into several different antigenic proteins by electrophoresis under native conditions (mol.wt. 80-400 kD; most immunoreactive components, 80-120 kD) or after isoelectric focussing (pI 5.8-7.4). After 2-dimensional electrophoresis followed by migration in a polyacrylamide-SDS gel, (A) appears as a 40 kD protein. The material from rat oesophageal epithelium is resolved into 3 components by 2-dimensional electrophoresis (migration (as above). 210kD (pI 5.85-6.85); 90-130 kD (pI 5.85-7.35) and 67-120 kD (pI 5-7.5).

USE - (A), and its fragments, are useful (1) for detecting AAb in body fluids by usual immunoassay methods; (2) for affinity purifn. of AAb; and (3) for raising **antibodies** (which can then be used to produce anti-idiotypic **antibodies**). Human (pro)**filaggrin** (or its fragments) can also be used for diagnosis of PR. The **antibodies** can be used to study immune proceses involved in PR and therapeutically

Dwg.0/17

FS CPI EPI

FA AB

MC CPI: B04-B04C2; B11-B; B12-D03; B12-K04A; D05-H07; D05-H09; D05-H13; J04-B01B
EPI: S03-E14H4

ABEQ FR 2681600 A UPAB: 19931116
Prepn. contains an antigen with the following properties: (1) can be extracted from human epidermis or rat oesophageal epithelium; (2) is a water-soluble protein; (3) its immunoreactivity is not affected by treatment with nuclease, EtOH or trichloroacetic acid and (4) is specifically recognised by **autoantibodies** (AAb) present in patients with **rheumatoid polyarthritis** (PR).

Also new are individual antigenic components of (A), or of human (pro) **filaggrin**, able to recognise AAb.

(A) from human epidermis is pref. sepd. into several different

antigenic proteins by electrophoresis under native conditions (molecular wt. 80-400 kD; most immunoreactive components, 80-120 kD) or after isoelectric focussing (pI 5.8-7.4). After 2-dimensional electrophoresis followed by migration in a polyacrylamide-SDS gel, (A) appears as a 40 kD protein. The material from rat oesophageal epithelium is resolved into 3 components by 2-dimensional electrophoresis (migration (as above).210kD (pI 5.85-6.85); 90-130 kD (pI 5.85-7.35) and 67-120 kD (pI 5-7.5).

USE - (A), and its fragments, are useful (1) for detecting AAb in body fluids by usual immunoassay methods; (2) for affinity purifn. of AAb; and (3) for raising **antibodies** (which can then be used to produce anti-idiotypic **antibodies**). Human (pro)**filaggrin** (or its fragments) can also be used for diagnosis of PR. The **antibodies** can be used to study immune processes involved in PR and therapeutically.

Dwg.0/19

=> d his

(FILE 'HOME' ENTERED AT 09:00:42 ON 14 MAR 2002)
SET COST OFF

FILE 'REGISTRY' ENTERED AT 09:01:01 ON 14 MAR 2002
E FILAGGRIN
L1 6 S E3
L2 10 S ?FILAGGRIN?/CNS
L3 10 S L1,L2

FILE 'HCAPLUS' ENTERED AT 09:01:52 ON 14 MAR 2002
E FILAGGRIN
L4 325 S E3-E5
L5 4 S E11
L6 326 S L4,L5
E FILAGGRIN/CT
E E3+ALL
L7 240 S E4,E5,E3+NT
E FILAGGRIN/CT
L8 31 S E4,E5
E E4_ALL
E FILAGGRIN/CT
E E4+ALL
L9 81 S E4-E6
L10 339 S ?FILAGGRIN?
L11 340 S L6-L10
L12 8 S L3
L13 341 S L11,L12
E SERRE G/AU
L14 40 S E3-E5
E GIRBAL NEUHAUSER E/AU
L15 10 S E3,E4
E GIRBAL E/AU
L16 4 S E3,E4
E NEUHAUSER E/AU
L17 9 S E3,E4
L18 5 S E10
E VINCENT C/AU
L19 360 S E3-E14,E32,E33
E SIMON M/AU
L20 826 S E3-E28
E SIMON MICHEL/AU
L21 94 S E3-E6
E SEBBAG M/AU
L22 18 S E3,E4
E DALBON P/AU
L23 26 S E3-E5
E JOLIVET REYNAUD C/AU

```
L24          37 S E3,E4,E1
                E JOLIVET C/AU
L25           5 S E3
L26           1 S E53
                E REYNAUD C/AU
L27          76 S E3,E4,E12
                E ARNAUD M/AU
L28         147 S E3-E9,E20
                E JOLIVET M/AU
L29          92 S E3,E4,E8,E9
                E  BIOMOERIEUX/PA,CS
                E  BIOMERIEUX/PA,CS
L30         195 S E3-E36
L31         134 S (BIO(L)MERIEUX)/PA,CS
L32          21 S L13 AND L14-L31
L33           8 S L32 AND ?CITRUL?
L34           4 S L32 AND ARGIN?
L35           0 S L32 AND (CIT OR ARG)

    FILE 'REGISTRY' ENTERED AT 09:12:02 ON 14 MAR 2002
L36           2 S ARGININE/CN
L37           1 S D-ARGININE/CN
L38           1 S CITRULLINE/CN
L39           2 S (DL-CITRULLINE OR D-CITRULLINE)/CN

    FILE 'HCAPLUS' ENTERED AT 09:12:47 ON 14 MAR 2002
L40       31077 S L36-L39
L41           4 S L40 AND L32
L42           8 S L33,L34,L41
L43          14 S L13 AND L40
L44          26 S L13 AND (CIT OR ?CITRUL?)
L45          27 S L13 AND (ARG OR ARGIN?)
L46          17 S L44 AND L45
L47          23 S L43,L46
L48          13 S L43-L45 NOT L47
L49          36 S L42-L48
L50          30 S L13 AND ?RHEUMAT?
L51          30 S L13 AND ?ARTHRIT?
                E RHEUMAT/CT
                E E19+ALL
L52        8601 S E9,E10,E8+NT
                E E19+ALL
L53        1292 S E4
                E E6+ALL
L54       16375 S E5+NT
                E E4+ALL
L55       18146 S E4,E5,E3+NT
L56          26 S L13 AND L52-L55
L57          30 S L50,L51,L56
L58          28 S L13 AND AUTOANTIBOD?
L59           7 S L13 AND AUTO(L)ANTIBOD?
                E AUTOANTIBOD/CT
                E E4+ALL
L60           8 S E1 AND L13
L61          13 S E2 AND L13
L62           9 S AUTOANTIB?/CW AND L13
L63          91 S ?ANTIBOD? AND L13
L64          91 S L58-L63
L65         110 S L57,L64,L49
L66          80 S L65 AND (PY<=1998 OR PRY<=1998 OR AY<=1998)
L67          21 S L66 AND L49
L68          16 S L66 AND L57
L69          68 S L66 AND L64
L70          19 S L69 AND L67,L68
L71          31 S L67,L68,L70
L72          14 S L32 AND (PY<=1998 OR PRY<=1998 OR AY<=1998)
```

```
L73          35 S L71,L72
L74           7 S L32 NOT L73
L75          35 S L73 AND L4-L74
L76           7 S L74 AND L4-L75

     FILE 'HCAPLUS' ENTERED AT 09:22:24 ON 14 MAR 2002
L77          42 S L75,L76
                SEL HIT RN

     FILE 'REGISTRY' ENTERED AT 09:23:13 ON 14 MAR 2002
L78           3 S E1-E3
L79           2 S L78 AND L36-L39

     FILE 'REGISTRY' ENTERED AT 09:23:33 ON 14 MAR 2002

     FILE 'BIOSIS' ENTERED AT 09:23:48 ON 14 MAR 2002
L80           1 S L3
L81         625 S L6 OR L10
L82         625 S L80,L81
L83          20 S L82 AND (SERRE G? OR GIRBAL ? OR NEUHAUSER ? OR VINCENT ? OR
L84           0 S L82 AND (BIOMERIEUX? OR BIO(L)MERIEUX?)/CS
L85           1 S L83 AND BOOK/DT
L86         510 S L82 AND PY<=1998
L87          15 S L86 AND (L36 OR L37 OR ARG OR ARGIN?)
L88          10 S L86 AND (L38 OR L39 OR CIT OR CITRUL?)
L89           8 S L87 AND L88
L90           9 S L87,L88 NOT L89
L91          22 S L86 AND (?RHEUMAT? OR ?ARTHRIT?)
L92           3 S L91 AND L87,L88
L93          34 S 180?/CC AND L86
L94         124 S 345?/CC AND L86
L95         124 S ?ANTIBOD? AND L86
L96           0 S ?ANTI BOD? AND L86
L97          28 S L94,L95 AND L91,L93
L98          42 S L87-L92,L97
L99           8 S L93 NOT L98
L100         42 S L85,L98

     FILE 'BIOSIS' ENTERED AT 10:05:02 ON 14 MAR 2002

     FILE 'WPIX' ENTERED AT 10:05:28 ON 14 MAR 2002
L101         16 S ?FILAGGRIN?
                E FILAG
L102         15 S E5,E6,E9
                E FILIG
L103          2 S E4
                E FILLAG
L104         18 S L101-L103
L105          6 S L104 AND (?CITRUL? OR CIT OR ARG OR ?ARGIN?)
L106          6 S L104 AND (?ARTHRIT? OR ?RHEUMAT?)
L107          4 S L104 AND (P421 OR P423 OR P420)/M0,M1,M2,M3,M4,M5,M6
L108          9 S L104 AND ?ANTIBOD?
L109          0 S L104 AND ?ANTI BOD?
L110         18 S L104-L108
                SEL DN AN 4 9 10 11 12 15
L111          6 S L110 AND E1-E17
L112         12 S L110 NOT L111
L113          5 S L104 AND (SERRE ? OR GIRBAL ? OR NEUHAUSER ? OR VINCENT ? OR
L114          3 S L104 AND (BIOMERIEUX? OR BIO(L)MERIEUX?)/PA
L115          6 S L111,L113,L114

     FILE 'WPIX' ENTERED AT 10:17:02 ON 14 MAR 2002
```